# JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

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JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY
&
QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

# The Quest for Freud

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## I. ON FREUD'S GREATNESS

One hundred years have gone by, but the quest still continues.

The passage of time has intensified the effort to understand fully Freud's influence on many fields of human thought—history, art, pedagogy, and religion, as well as medicine—an influence that has spread like ever widening ripples in a disturbed pool.

A measure of extent of spread or the social importance of any human activity is the number of new words bequeathed to the common language of all nations. Modern language is studded with scientific neologisms. The medical ones are evidence of the generous contribution made by medicine to popular wisdom and the progress of civilization. Perhaps no other branch of medicine, not even the field of antibiotics, has added to the vocabulary of the writer, sociologist, and common man as much as Freud and psychoanalysis. Not only in literature but also in everyday language, a discerning ear can easily detect the familiar ring of psychoanalytic terminology.

Another key to a man's effect on the world about him is the gap separating the literature in his particular field of action published before and after his influence was asserted. The

breach between a book on psychiatry written prior to 1900, when Freud announced some of his most important discoveries, and a book on psychiatry today is indeed astounding. The enormous progress in psychiatry evidenced in this last half century due to Kraepelin, Cajal, Pavlov, Sherrington, Bleuler, and Freud is such that the gap is wider than that between any two books on psychiatry written in the prior 2000 years.

Today, over the face of the world, men of culture as well as men of medicine commemorate the centennial of the birth of the man who conjured up a new method of psychologic research, who gave mental hygiene so much of its modern form, and who wielded so great an influence on art, sociology, religion, and anthropology.

An anniversary is sometimes merely an occasion for a man's admirers to flick off the dust that has collected on their hero's bust. With Freud, however, his thought and work are so dynamic and disturbing that his birthday should be a time for reappraisal of his contributions to science. It is also a moment for orthodox psychoanalysts—many of whom are more Freudian than Freud himself—to do more than place another crown of laurel on the pale forehead of the great Viennese thinker. They should join, not fight against, the efforts to integrate his contributions into the whole body of scientific medicine with the objectivity that brought all science to its present high level.

Was Freud a genius?

Genius is made up of intuition, efficacy, and effort and is the happy compounding of three contingencies: intellectual aptitude, a suitable ground for such aptitude to flourish (for genius can be good only if it finds a favorable environment), and the right historical moment. If these three factors (aptitude, place, and time) do not occur together, genius can wither away unheard, unhonored, and unsung. These three essential factors did coincide in Freud's case.

Freud was a great man, and greatness is often combined with genius. During his lifetime, Freud possessed the insight of the great. His personal conviction was reflected in his reply to Princess Marie Bonaparte when she graciously reminded him that he was a great man; "I am not a great man; I merely made a great discovery."

Despite this apparent modesty, Freud nursed a vision of greatness throughout his life. It is said that the midwife attending his birth foretold his future triumph, and that her augury stayed with him and gave him inspiration all the years of his life. His own words after having made his mark indicate the influence he attributed to the opinion of those dear to him: "A man who has been the unquestioned favorite of his mother retains through his whole life the feeling that everything must yield to him, thus engendering that confidence in success which is frequently the determinant of success itself." Freud's career made a reality of the fireside prophecies of his genius. Today there are few who begrudge him the recognition that he coveted so much.

Freud always considered himself a child of destiny. The man who "knows" he has a mission in life is filled with a supreme impatience to fulfill it. Freud was anxious to reap his destiny while he was still alive. "I want no posthumous glory," he said on one occasion. That is the why of his creative haste. At the root of his genius also lay the power of his will. His concentration on his desire to create was one of the secrets of his whole existence.

"History," said Emerson, "is the biography of Greatness," because "man just waits, but genius acts." Thus true greatness is man's forestalling of immortality. To be great is to live in perpetual defiance of what is close by and in everlasting search of what is eternal and universal in man.

Looked at in this light, History is not a journey through darkness but an exploration for the torch of creation in the primeval jungle of the human mind. The ordinary man feels himself restricted spatially by his biology and chronologically by the shortness of his life. The genius, however, knows that his dreams are sufficiently powerful to become reality propelled by his creative *élan*, which draws its energy and motive power from that infinite reservoir of the mind that every human being possesses. For, as Cajal remarked, "Geniuses, like abyssal creatures, move on illuminated by their own inner light."

SIGMUND FREUD

No one can possibly object to the attribution of genius to Einstein. His was the genius that knew how to discover and reveal a new fragment of the universe, how to formulate a lineage of *objective* problems and then point the way to their accurate solution. Such discovery of universal facts and objective truths was the work of a Newton or a Max Planck. But when the creation is the fruit of a *subjective* act, as was the case with Freud, should the palm of genius be awarded in this instance also?

Perhaps we can get at the answer if we consider the case of Descartes, whose philosophic thinking is still the cornerstone of the modern scientific world. His was an eminently subjective creation, but its fundamental validity was ultimately revealed as a universal objective truth. It may be the same with Freud. We trust that his original ideas were more than a subjective imagining, that they did more than burgeon out of some mystic enlightenment. Were they not the fruit of his naturalistic observation of man as he saw him wending his way along the cold corridors of the Salpêtrière or in his modest office in the Berggasse?

Is great fertility a characteristic of genius? There is one group of geniuses whose immortality rests on more than a single scientific discovery, a single literary masterpiece, or a lone immortal symphony—Leonardo da Vinci, Goethe, Balzac, and Rembrandt. Of those who are remembered for only one particular discovery or invention, e.g., Fleming for penicillin, Cervantes for *Don Quixote*, Helmholtz for his optics, if we examine the setting of their "one" great thing, we soon realize that that particular thing was an accomplishment of such outstanding brilliance as to outshine all the rest. Their other discoveries, being less brilliant,

are overlooked despite their value or the continuity and directed effort they gave to a creative life.

In Freud's case, his interpretation of dreams ought not to obscure his other psychologic formulations, just as his concept of psychoanalysis ought not to blind us to his broader understandings or confine to limbo his labors in the pharmacologic and neurologic fields which filled out the confines of his life.

Freud's concepts burst upon a stodgy Victorian world at the end of the nineteenth century, with its cult of individualism and of will power, the "I am the master of my fate; I am the captain of my soul" of W. E. Henley.

Freud's ideas on the unconscious motivation of our thoughts and deeds excited much irritation in his time— a time when middle-class society lived a commonplace, genteel public life (apparently in harmony with middle-class conventions), with a private life ruled by the principle of pleasure.

Freud set himself up against all that this represented. His interpretation of neuroses was in reality a condemnation of the historical backsliding of middle-class society in Victorian Europe. The general reaction was unanimous, and Freud's doctrines were "officially" proscribed.

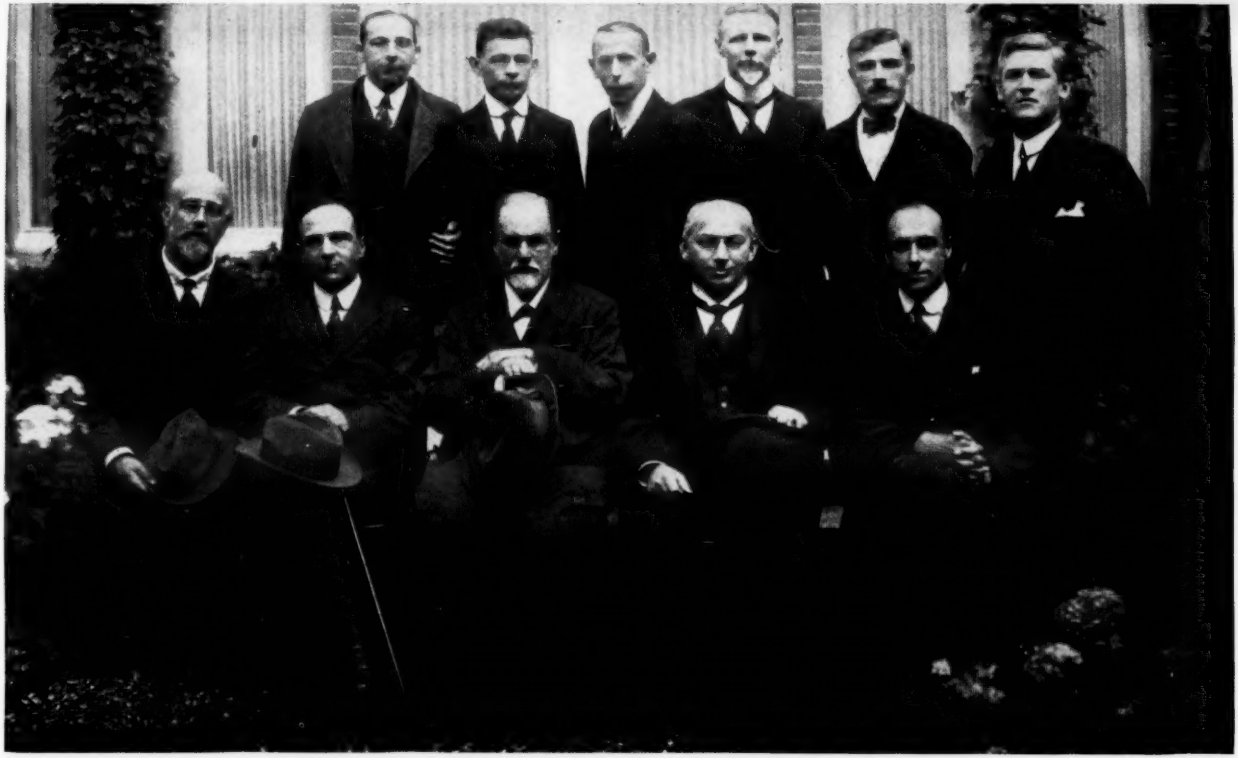
Some men attain glory by discovering a single drug. Freud contributed new *principles*. These principles afford us a key to Freud's greatness, to his contribution not only to psychiatry but also to modern medicine in general.

## II. FREUD'S SCIENTIFIC ENVIRONMENT: CHARCOT AND KRAEPELIN

A proper understanding of Freud's work cannot be achieved without knowing the surrounding circumstances in which it was developed.

The latter half of the nineteenth century was of tremendous importance to the whole world of science. The great events—discoveries or confirmations of discoveries—that occurred in that period fill a stirring page in the history of science: the physical theory of the conservation of energy; the theory of evolution; the cell doctrine; the glycogenic function of the liver; the neuronal theory; conditional reflexes; the chemistry of metabolism; chemotherapy and biochemistry; the microbial origin of infection; immunity; the quantum theory; the structure of the atom; the rediscovery of Mendelian heredity; and the integration of the nervous system. As this epochal half century of discovery was coming to its close, Freud brought forth his interpretation of dreams and laid the beginnings of psychoanalytic concepts.

Psychiatry in the nineteenth century was in the process of becoming an autonomous discipline. The "natural" hippocratic theory on psychopathologic alteration had held sway for 2000 years. As late as 1765, Anne-Charles Lorry still held, as did Hippocrates, that alterations in the bile (to which Lorry added the elasticity of the organic "fibers") were responsible for insanity. Then, in the first half of the nineteenth century, French psychiatry (Pinel, Esquirol, Georget) became established on a structure somewhat like that of medical pathology. Mental diseases were classified in the manner reminiscent of the chapters of medical pathology prior to Sydenham. Only much later was the idea of the evolu-



Sixth International Psychoanalytical Congress, Den Haag, September 8–11, 1920.

Top row, left to right: H. Sachs, O. Rank, K. Abraham, A. F. Meijer, A. Stern, J. H. W. van Ophuijsen. Bottom row: J. E. G. van Emden, E. Jones, S. Freud, S. Ferenczi, J. C. Flugel. Dr. J. H. W. van Ophuijsen later (1950) became Editor of the Journal of Clinical & Experimental Psychopathology and founder and director of the van Ophuijsen Center (New York City) and of the Creedmoor Institute for Psychobiologic Studies.

tionary process—disease in the time dimension—added to the concept of the morbid species —disease in space.

On to this stage stepped Charcot (a fine observer of clinical pictures), in his own words a "Visual." In his time, hysteria was the condition that expressed most the "personal state" of the patient. The future psychosomatic approach had roots in his study of hysteria and of other neuroses. Charcot devoted 10 years of his life (1883 to 1893) to the grouping of hysteria symptoms. He studied them nosographically as a morbid species, and also pathogenetically, and concluded by classifying hysteria—until then considered a functional disease of the brain—as a psychoneurosis, in other words, as a functional disturbance psychically induced. It was at this point that Freud entered on the scene.

Charcot "saw" the motion of hysterical symptoms in time, "anatomy in motion"; Freud was interested in their *nature*. The cause of neuroses appeared to Freud as "a repressed affection" and "vital instinct" as libido.[2] Future historians have the task of ascertaining how much influence the repressed, puritan, middle-class society of Vienna in Freud's time had in setting ablaze the spark of his revolutionary theories. Even if Freud's postulate of the origin of neuroses appears like a sudden flash of inspiration, since every human idea is born from previous ideas, we must render due tribute to Charcot and recall his favorite phrase, which Freud heard so many many times while at the Salpêtrière: *"Mais, dans ces pareils c'est toujours la chose genitale, toujours, toujours, toujours."**

But if Charcot restricted his thinking to the dramatic theater of the hysterical cases at the Salpêtrière, Freud's thinking started off with the enunciation of an empiric theory on neuroses to which he added further postulates until he even encompassed a speculative theory of religion and culture. Perhaps Freud was driven by the idea he had of himself—based on a phrase borrowed from Hebbel—of having "disturbed the sleep of the world."

Furthermore, we must not forget the effects of German ideas on psychiatry, as well as the French, in the early years of Freud's work.

The psychobiologic trend of the fifteenth to nineteenth centuries was pushed back by the wave of histopathology aroused by Virchow. The dictatorship of the microbe ruled in medicine. Certain voices were being raised: Darwin (1873) in describing emotional reactions as an important biologic phenomenon; Cannon in his two basic works (1911, 1915) on the study of the physiology of the emotion; Oliver Wendell Holmes in his "Medicated Novels" (1859–1885); and others who dared to set up the role of suggestion and bodily emotions in contraposition to the all-powerful etiologic empire of the microbe.

Kraepelin's nosographic work, chronologically contemporary with Freud's, historically came before Freud's. He sought to convert the then existing psychiatric chaos into an ordered, even though arbitrary, cosmos. Though his ideas were ridiculed by some as an "imperial German psychiatry" because of their didactic rigidity, nevertheless through him psychiatry advanced its evolution from a philosophic discipline toward a natural physical science, to become more intrinsically part and parcel of the science of medicine. Thanks to

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* "But in these and similar cases, it is always a genital (sexual) matter, always, always, always."

Kraepelin the working methods of the psychiatrist began to acquire an organization along lines similar to the methods practiced in clinical medicine.

Although they were contemporaries, Freud took a different path than Kraepelin did. Psychologically, they were antipodes for, while Kraepelin sought objective systematization, Freud probed subjectively and his psychoanalysis is the "literary" aspect of psychiatry. Freud was a romantic,* despite the fact that he was trained by some of the greatest purely scientific teachers of his time—Billroth, Arlt, Claus, Brücke, Meynert, Nothnagel—and that he was an associate of Wagner-Jauregg, the first psychiatrist to win a Nobel prize.[2] Freud's romanticism is reflected by the fact that, while for Charcot an *idea* could originate psychosomatic symptoms, for Freud the cause of such symptoms was an *emotion* or feeling.

Among the main factors that went into the formation of new theories in neuropsychiatry, it is important to note three new concepts formulated during that time: John Hughlings Jackson's "evolution and dissolution," Sherrington's "integration," and Freud's "repression."

### III. THE CONTRIBUTIONS OF FREUD TO MEDICINE

The historical chronology of psychoanalysis is well known. In May, 1896, Freud explained, based on his previous work with Breuer, his interpretation of dreams and used the word *psychoanalysis* for the first time to denote a method of inquiry, a doctrinal corpus, and a special therapeutic technique.

Up to 1902 Freud worked alone, investigating the psychology of the unconscious, reporting many of his observations in his strange and fascinating correspondence with Wilhelm Fliess. In 1902 he formed his first group of followers, among them Adler, Rank, and Jung. In 1908 Freud met with his followers in Salzburg, and in 1910 the International Association of Psychoanalysis was founded. From then until 1930, when interest in psychoanalysis began to decline somewhat, Freud saw his principles grow and develop and extend to other fields of medicine.

Freud was interested in etiology, pathogenesis, nosography, and mental therapy. He divided etiopathology into *conditional* (hereditary), *concurrent* (emotions, stress, traumas), and *specific*. Ignoring the existing nosographic descriptions, he passed from nosologic to personal diagnosis. As basic therapy he accepted catharsis and transference. Integrating psychologic study with psychiatric clinics, he focused attention on the world of the unconscious, sought to evaluate psychogenic factors, built theories of psychodynamics, and added new values to the clinical case history.

Prior to Freud, diseases were considered morbid cysts in the external life history of the person. After Freud psychopathography became an integral part of the patient's biography, for Freud included the patient's inner life in anamnesis, making of the patient a *person*. Thus he began his most important contribution to medicine, which was to help link more closely psychiatry with anthropology.

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* As literary precursors for his work, Freud had the great Greek and Shakespearian tragedies, Zola's naturalism, Mallarmé's romantic symbolism, and Nietzsche's philosophy.

With Freud, the technique of association became a basic method of investigation; the Hippocratic interrogation was broadened by a dynamic interview in which both the patient and the physician, instead of only the latter, are active participants. This serves to dig more deeply into the intimate, inner life of the patient, who ceases thereby to be a mere witness and becomes also an *interpreter* of himself. Pathography thus becomes *biography*, combining not only the environmental factor and the pathophysiologic facts but also the patient's unconscious instincts.

Psychoanalysis advanced the clinical case history because it stressed associative speech as an instrument of exploration and therapy. Freud was an "auscultator" of dialogues.

"Behavior is a mirror in which everybody reflects his image," said Goethe. For Freud, the truest mirror of the mind was the spoken word. Mental pathology with him ceased to be visual and became *auditive*. Before Freud, anamnestic dialogue was merely declaratory; the patient related things of which he was a passive witness. Freud made anamnesis into an *interpretative* art; the patient interpreted his life and the physician *interpreted* the patient's own interpretation. Freud therefore turned the spoken word not merely into a research instrument but also into a therapeutic agent.

Freud's word turned into metaphor, and metaphor is the enemy of dogma. Such metaphor was for him expressive of an instinctive, eminently erotic, existence. Man was for Freud *homo sexualis*, in whom the word could become a cathartic agent, just as it was, in the religious and medical sense, in the classic Greek *katharsis*.

Elsewhere we have mentioned the contributions made by psychoanalysis to modern medicine, to wit: first, engaging in dialogue with the patient in order to integrate the event of disease in his biography; second, the therapeutic and diagnostic evaluation of the instinctive factor in human life as an intermediate link between the body and the ego (perhaps foreshadowed in Sydenham's *inner man*) and the influence that mental life exerts on the mechanics of the body; third, the discovery and interpretation of the various levels of psychologic consciousness and the influence of the subconscious and the unconscious on a person's life.

Freud had started as a biologist and a scientist; thus, though he used an "old" tool, the word, for exploring his special domain, his interpretations tended toward the mechanistic and even his own vocabulary belonged more to physics than to psychology. His concept of "the instincts" was that they were *qualitatively* equivalent while their disturbances depended on *quantitative* variations. His phraseology—"condensation," "displacement," "repression," etc.—seems to have been borrowed from the semantic arsenal of physics.

## IV. WAS FREUD A SCIENTIST?

The basic formative years of Freud's career were spent in a scientific atmosphere, steeped in pathology and pharmacology. Freud's first scientific task was in zoology, dissecting 400 eels to confirm, at the behest of his instructor Claus, whether the small lobulate organ discovered by the Pole Syoski (1874) was the until then unheard of testes of the eel.

Did Freud prefer to be a medical practitioner or a scientific investigator? He stated, "After 41 years of medical activity, my knowledge of myself tells me that I have never

really been a doctor in the true sense of the word. I became a doctor because circumstances compelled me to diverge from my original intention. I do not recall whether in my childhood I ever had the least desire to aid humanity . . ." These rather ruthless words belie the great service to mankind of a man who gave so intensely in his search for knowledge. On another occasion Freud stated, "I am not really a man of science, not an observer, not an experimenter and not a thinker. I am nothing but by temperament a Conquistador—an adventurer if you want to translate the word—with the curiosity, the boldness and the tenacity that belongs to that type of being."

We know that Freud labored greatly on problems of pathology and pharmacology during his more youthful years. He investigated the medulla oblongata of the lamprey with Brücke, the nuclei of grey matter and fibers of the human spinal bulk with Meynert, and the properties of cocaine with Fliess.

As an investigator without a laboratory, Freud turned his office into his laboratory and each patient into an object of study. By the application of naturalistic observation, his clinical interrogations became psychologic studies.

Freud's fundamental scientific honesty is expressed by his counsel that the best attitude to take in psychoanalysis is one of "benevolent skepticism." The force of his personality, however, was such that it unfortunately made many of his followers not pupils but proselytes who turned doctrine into dogma. Freud gave new directions to clinical medicine and to psychiatry, whereas the dogmatism of his fanatic followers has hindered the progress of a truly scientific psychiatry.

Freud hoped for the day when psychology, endocrinology, and neurophysiology would be integrated, as when he asserted, "All our provisional ideas on psychology will some day be based on an organic substructure . . . This brings up the possibility that special substances and special chemical processes may control the mechanics of sex, allowing the continuity of individual existence within the species."[18]

Freud loved science. Though science today is becoming a discipline of organization and teamwork, in the time of Freud scientists still worked alone and had to be endowed not only with genius but also with courage, determination, self-discipline, and a spirit of self-sacrifice to be able to set out on the long, lonely, uncertain road of investigation. All these qualities Freud possessed in the highest degree.

Freud was also a true teacher. A true teacher knows above all how to inspire and to give. Freud, who has been accused of being merely a divulgator, a "transmitter" in the Oslerian sense, was a true teacher. Unamuno said, "To divulgate is also to create." Freud did more than create, he propagated and communicated.

### V. FREUD'S CONTRIBUTION TO THE KNOWLEDGE OF MAN

Freud's revival of the ancient rituals, the Assyrian method of questioning directed at the patient's memory and inmost thoughts, did more than vindicate the "personalism" of the ancient Semitic medicine. It made psychiatry, and then medicine in general, concentrate upon another aspect of the patient. Thanks to Freud, the patient became more of a multidimensional organism in the eyes of the physician.

The clinician for centuries had been treating his patients, sometimes with considerable success, as a biologic mechanism. Sydenham, Trousseau, and Osler did that. The medical pathologist looked upon his patient as a physical object or as a disturbed biologic entity. Freud was among the first to compel medicine to examine the patient more as a historical and sociobiologic organism.

As against the concept of *homo aeternus* or *homo coelestis*, Freud was interested in *homo natura* and wished to define his psychology, introducing in the study of mental diseases anthropologic and "auditory" attitudes.

Freud's conceptions of man as a biologic and historical organism inspired his hypotheses that sought to explain psychologic phenomena. In this task Freud was interested more in *why* his patients were suffering than in *what* they were suffering from, in the forces responsible for their complaints, stresses, and changes in the mysterious mechanics of his theoretic entities—libido, eros, and aggressive and death instincts. The concepts have done much to mold the image that the Western man of today has of himself and have deeply influenced modern literature, just as Claude Bernard's work influenced Zola and much of the literature of his time.

Rebelling against the Hegelian interpretation that identified the rational with the real, Freud adopted an arrogant Dionysiac pose, asserting the will to love and have power in a Nietzschian manner and formulating such concepts as his "geological" view of the mind and his "deep psychology," deeply rooted in the psychology of Nietzsche.

Whereas Nietzsche and Kierkegaard conceived of a psychology that was isolated at topmost spiritual heights, Freud originated a psychology that is universal in its acceptance.

Before the first World War, medical thought followed the lines set down by Johannes Müller and Claude Bernard to the effect that "pathology is nothing but disturbed physiology" and gave the laboratory pride of place over the hospital. The *extrasomatic* factors—social, historical, and psychologic—of the individual had yet to become prime subjects for study. The newer biographic and anthropologic concept of illness is today of the greatest importance in clinical medicine. Freud's contribution to this development may be among his most significant and may successfully integrate Claude Bernard's basic principles into the spatial and temporal components of man's life.

## L'ENVOI

These thoughts, hovering around the figure and the work of Freud, are our tribute on his birth centennial.

Today psychiatry stands on the threshold of a new era. Biochemistry, metabolic research, endocrinology, neurophysiology, pharmacology, and nuclear physics—all may help to open wide the doors and let in the light that will dispel the shadows in which our knowledge of mental disease has dwelled for so many centuries. It is therefore now more important than ever to recall the true stature of Freud, which transcends the narrow limits of psychoanalysis.

To keep pace with scientific progress, to renounce the fanaticism of dogma and sect, to rectify when beliefs are exposed as mistakes, and to regard properly the complex wonder of health and sickness, the psyche and the soma, not with the limited instrument of a single theory or a single technique, even though it may be remarkable as psychoanalysis was, but with every available scientific tool—these afford the best way to honor the memory of Sigmund Freud. The adoption of such an integrated attitude in psychiatry may bring the best success in the quest for the greatness of Freud.

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# Dr. Félix Martí-Ibáñez Appointed Professor of History of Medicine and Director of New Department by New York Medical College

New York Medical College, Flower and Fifth Avenue Hospitals, recently appointed Félix Martí-Ibáñez, M.D., director of their new History of Medicine Department. It was also announced that Dr. Martí-Ibáñez will serve as Professor of the History of Medicine.

Dr. Martí-Ibáñez, a writer and medical historian, is the Associate Editor of ANTIBIOTIC MEDICINE & CLINICAL THERAPY, International Editor of ANTIBIOTICS & CHEMOTHERAPY, Editor of the INTERNATIONAL RECORD OF MEDICINE, and International Editor of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY.

Born in Cartagena, Spain, Dr. Martí-Ibáñez studied at the Medical School of the University of Barcelona and received his Doctorate in Medicine from the University of Madrid. Until 1939, he practiced psychiatry in Barcelona and taught medical history. He also edited several medical and literary journals and published two novels and several books on the history of medicine, psychology, and eugenics.

In 1937 Dr. Martí-Ibáñez was appointed General Director of Public Health and Social Service of Catalonia, and later became Under-Secretary of Public Health and Social Service in the Spanish Government. He officially represented Spain at the World Peace Congresses held in Geneva, New York, and Mexico City. He was wounded while serving as a major in the Medical Corps of the Spanish Air Force.

After his arrival in the United States in 1939, Dr. Martí-Ibáñez held positions as Medical Director with three leading pharmaceutical concerns. He also lectured in many Latin American universities and was made an honorary member of fifteen medical, historical, and psychiatric associations.

He participated in the International Congresses of History of Medicine, History of Science, Psychology, and Psychiatry held since 1950 in Amsterdam, Paris, Stockholm, Nice, and Rome, and he has published many papers on psychiatric and medical-historical subjects in American and European medical journals.

A Fellowship was awarded to Dr. Martí-Ibáñez by the American Medical Writers' Association at their annual meeting last year. Also, he was recently honored, by unanimous decision of the National Academy of Sciences of Cuba and by decree of the Government of Cuba, with the Order of Carlos J. Finlay in recognition of his scientific and educational work in medicine. He is a member of the Foreign Press Association and the Stage and Screen Foreign Press Club and contributes columns to Latin American newspapers. Articles and short stories by Dr. Martí-Ibáñez have appeared in *Esquire, Town and Country, Gentry, Art & Architecture,* and fantasy story magazines.

INTERNATIONAL SYMPOSIUM ON CHLORPROMAZINE

PART II*

# Neurophysiologic Activity of Chlorpromazine in Clinical Use

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Within five years of its first clinical application, chlorpromazine has been administered to millions of patients in many countries and has been the subject of more than one thousand publications. The drug was developed in France by Rhône Poulenc, as a result of a systematic search for a phenothiazine derivative with the most specific action on the central nervous system. The impetus for that search had come from Laborit[1] who had foreseen the tremendous potentialities that might lie in a pharmacologic agent capable of temporarily suspending the defensive responses of an organism to stress. Laborit had noted that these defensive adjustments frequently tend to become excessive, constituting a secondary stress that may prove to be more perilous than the primary trauma. As so often happens in the history of medicine, an original hypothesis led to the discovery of a new therapeutic agent whose action exceeded original expectations, although the theory that motivated the original research was no longer capable of accounting entirely for the therapeutic results.

The principal action of chlorpromazine is on the central nervous system. This accounts for its antiemetic effect, its usefulness in cases of persistent hiccup, the relief of intractable pain in terminal cancer, its effectiveness in anesthesia, and its therapeutic value in states of marked emotional tension, or in acute or chronic psychotic conditions.

The most powerful therapeutic impact of chlorpromazine was felt in psychiatry. In 1952, Delay et al[2] published their first systematic observations on the effectiveness of the drug in states of manic excitement. Their original observations were soon confirmed by others.[3–6] It was found that chlorpromazine was capable of producing remissions in many acute psychotic conditions such as the manic phase of manic-depressive psychosis, schizophrenia, various paranoid conditions, and toxic confusional states. To everyone's amazement, it was also capable of producing remissions in a considerable number of chronic psychotics, some of whom had been refractory to other treatments and had been relegated to the back wards of mental hospitals as "incurables."[7, 8] A therapeutic feature introduced

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* Part I of this Symposium appeared in the January-March issue. Part III will appear in the July-September, 1956, issue.

into psychiatry for the first time by chlorpromazine was that the drug now made it possible to carry out effective maintenance therapy in a number of psychotic patients who could function without incapacitating symptoms as long as the drug was administered, but who would relapse into a severe psychotic state when chlorpromazine was discontinued.[9, 10] Such an agent had not been known before and came as a surprise to most psychiatrists.

The clinical usefulness of chlorpromazine has been established and confirmed beyond any doubt. An important task remains to be done: to develop a rationale, a theoretic basis for the clinical action of the drug that will allow the clinician both to limit and to extend the use of the drug, basing his decisions on meaningful principles instead of on mechanical techniques or random trial and error procedures. It is the purpose of this paper to review the neurophysiologic activity of chlorpromazine as established by animal experiments and clinical observation, as well as the theories offered to explain its action, in order to gain a vantage point from which we may formulate a rationale of its therapeutic effectiveness.

## PHARMACOLOGY

A complete review of the pharmacology of chlorpromazine is not within the scope of this paper. Several extensive reviews are available.[11–13] This article will concern itself mainly with the effects of the drug on the central and autonomic nervous systems.

One of the first significant actions of chlorpromazine to be observed is its strong potentiating effect on most cerebral depressants, i.e., hypnotic, analgesic, and anesthetic substances. Chlorpromazine alone will not produce hypnosis or general anesthesia, though it markedly inhibits psychomotor activity in animals and man. In animals, it consistently produces hypothermia, while in man its effect on the thermoregulatory system is less predictable. The drug strongly inhibits vomiting and nausea in animals and man.

One of the most characteristic properties of chlorpromazine is its pronounced sympathicolytic action. It inhibits the peripheral and central effects of adrenalin, except for the increase of blood sugar. Noradrenalin is not as effectively blocked by the drug. Clinically, this inhibition of adrenergic functions is reflected in a fall of systolic blood pressure following the administration of chlorpromazine. It also possesses some antiacetylcholine properties, particularly in higher doses, which account for the clinically observed dryness of the mucous membranes, tachycardia, and a tendency to constipation.

## NEUROPHYSIOLOGIC OBSERVATIONS IN ANIMALS

The action of chlorpromazine on the central nervous system of animals has been studied by various investigators who used one or several of the following three methods of analysis: (1) modifications of cerebral electric activity (electroencephalogram) by chlorpromazine under conditions of rest and stimulation; (2) modifications of the central and peripheral nervous responses induced by chlorpromazine in animals exposed to the effects of other active pharmacologic substances such as nicotine and adrenalin; and (3) modifications of the total behavior of the animal under the effects of chlorpromazine.

*Modification of the Electroencephalogram.* Das et al[14] showed that, following the adminis-

tration of chlorpromazine in rhesus monkeys, bursts of slow waves appeared in the electroencephalogram occasionally interrupted by low voltage alpha and beta activity. Optic, acoustic, or tactile stimuli led to sudden and momentary spike discharges. When doses of chlorpromazine exceeded 3 mg./Kg., sleep spindles appeared. One of the monkeys, however, whose behavior prior to and following the administration of chlorpromazine had been quite different from that of the other animals, showed spike and wave discharges after an intravenous injection of 2 mg./Kg. of chlorpromazine. The authors point to the striking resemblance between their findings and those of Magoun et al[15, 16] in monkeys following a surgical interruption of ascending influences from the brain stem reticular formation.

Longo et al,[17] working with normal and *encéphale isolé* rabbits, recorded the electroencephalogram through electrodes applied directly to the frontal, parietal, and occipital areas of the cortex, as well as from subcortically placed electrodes. Chlorpromazine caused an increase in the number of slow waves from all leads and an increase of the spindle bursts that are normally present in rabbit brains. The normal response to external stimuli, consisting in desynchronization of the electroencephalographic pattern and referred to variously as the blocking reaction, awakening or arousal reaction, or activation pattern,[18, 19] was diminished in the rabbit. Auditory or tactile stimulation no longer provoked this activation pattern, and only nociceptive stimuli (electric stimulation of the sciatic nerve) inhibited the "spindles" but did not lead to the appearance of a complete arousal reaction. This inhibition of the arousal reaction was obtained with doses considerably below toxic levels that did not affect any behavioral alteration in the normal animal.

Utilizing the *encéphale isolé* preparation with a transection of the spinal cord at C 1, these investigators found electroencephalographic responses exactly comparable to those described for the normal rabbit, and concluded that the influence on the arousal mechanism was exerted on superior structures and was independent of the action on the spinal cord and peripheral nervous system.

The same authors produced direct brain-stem stimulation in the curarized rabbit by stimulating the rostral portion of the reticular formation at the level of the anterior hypothalamus through a concentric electrode, and they obtained a modification of the electroencephalogram that was qualitatively similar to the arousal reaction elicited with sensory stimuli. After a dose of 3 mg./Kg. of chlorpromazine, the response in the corticogram to light hypothalamic stimulation was inhibited. Strong hypothalamic stimulation, however, still produced some desynchronization of the electric pattern. The authors point to the findings of Funderburk and Case[20] who described an analogous action of atropine on the electroencephalogram of the cat. Physostigmine proved to be very effective in counteracting the inhibition of the normal arousal reaction caused by atropine, chlorpromazine, and a group of other drugs that modify the electroencephalogram. This inhibition essentially involved a blocking of afferent pathways without apparent influence on behavior or reflexes. Other drugs such as amphetamine, serotonin, epinephrine, and acetylcholine were devoid of any antagonistic action.

Hiebel et al,[21] working with cats, observed the same effect of chlorpromazine, namely that 0.5 mg./Kg. of the drug led to the progressive disappearance of all rapid activity in

the electroencephalogram and to the appearance of irregular slow waves. The tracings did not in any way resemble those obtained after barbiturates. These authors also showed that the arousal reaction of the electroencephalogram to repeated olfactory or auditory stimulation was diminished and disappeared rapidly after the stimulation ended. In the normal animal, the arousal pattern continued for some time after the stimulus was discontinued. They also found that only the strongest electric stimulation of the reticular substance would evoke the activation pattern. While barbiturates and other cerebral depressants produce similar effects, the action of chlorpromazine differs in that an increase of dosage does not lead to anesthesia, nor does it ever produce the typical electroencephalographic pattern associated with barbiturates.

All experimental studies of the central action of chlorpromazine led to the same conclusions: (1) chlorpromazine inhibits fast potentials in the electroencephalogram; (2) it suppresses the mechanisms responsible for desynchronization of the electroencephalogram that are manifested in the arousal or awakening reaction; and (3) it raises the threshold for direct electric stimulation of the reticular-activating substance in the brain stem.

*Modification of Response to Other Drugs.* Chlorpromazine inhibits the convulsions and tremor caused by nicotine. Longo et al[17] showed that the administration of nicotine to the normal and *encéphale isolé* rabbit would produce electroencephalographic changes characteristic of a grand mal seizure. Chlorpromazine in doses of 5 mg./Kg. completely inhibits the electric patterns provoked by nicotine. Physostigmine causes the return of the normal arousal reaction to stimuli in the animal after chlorpromazine, but it does not reverse the inhibitory reaction of chlorpromazine on nicotine. Thus it is possible to dissociate the blocking action of chlorpromazine on the afferent pathways, which is also produced by atropine and counteracted by physostigmine, from its anticonvulsant properties with regard to nicotine-induced convulsions that are not sensitive to physostigmine.

Chlorpromazine does not antagonize convulsions produced by pentylenetetrazole, picrotoxin, and strychnine.[17, 22] This may be explained by the fact that one of the principal sites of action of these drugs is the cortex, while nicotine produces convulsions through its action on a chemoreceptor area in the midbrain.

Chlorpromazine has a pronounced blocking action on apomorphine-induced vomiting in dogs.[23, 24] It is assumed that apomorphine acts on chemoreceptor areas in the midbrain to produce vomiting, and that chlorpromazine has a specific inhibitory effect on this chemoreceptor.

Further experimental evidence of the blocking action of chlorpromazine on structures in the midbrain that are sensitive to humoral excitation has been provided by Hiebel et al.[21] These authors showed in cats that a peripheral injection of adrenalin would evoke an intense and generalized activation of the electroencephalogram. This effect still persists in a brain with a transection at C 1 (*encéphale isolé*), but disappears after a more anterior section of the brain stem, strongly suggesting that the central excitatory action of adrenalin takes place at the level of the pontomesencephalic portion of the reticular-activating substance. This central excitatory effect of adrenalin usually overshadows the suppressor action of the carotid sinus, which also responds to adrenalin in circulation. After an animal has received

chlorpromazine, the central excitatory effect of adrenalin on the reticular-activating substance is abolished, and the suppressor action of the carotid sinus reflex is allowed to supervene so that an increase of adrenalin in the circulation will actually lead to cerebral depression that may be reflected in a general slowing of the electroencephalogram.

Independently, Rothballer[25] has recently shown that a component of the reticular-activating system responds to adrenalin by producing an arousal reaction, and that the sensitivity of this area is reduced by chlorpromazine.

*Modification of Total Behavior.* All investigators agree that chlorpromazine produces marked inhibition of motor activity in animals, although hypnosis is usually not produced by the drug and anesthesia is never obtained. Tendon reflexes and postural reflexes can regularly be elicited in these animals whose behavior is characterized by pronounced akinesia.

In animals, chlorpromazine inhibits conditioned reflexes but does not abolish unconditioned avoidance reactions to noxious stimuli, as would result from sedation with barbiturates at the same level of depression.[26]

Dasgupta et al[27] could show that chlorpromazine suppresses sham rage in diencephalic cats more efficiently than affective behavior in intact animals, and they conclude from this that a central depressant effect of the drug on the activity of the cortex can be excluded. Das et al[14] gave chlorpromazine in doses of 0.7 to 2 mg./Kg. to 9 rhesus monkeys. Eight of the animals were very aggressive and easily displayed anger and ferocious behavior. The remaining animal was fearful and withdrawing, sitting quietly in one position when undisturbed. Following the administration of chlorpromazine, the behavior of all animals changed dramatically. The 8 aggressive rhesus monkeys became peaceful and docile, while the 1 animal who had been timid and quiet in the control period became wild and aggressive after 1.5 mg./Kg. of chlorpromazine. An increase of the dose to 3 mg./Kg. intensified these symptoms.

## NEUROPHYSIOLOGIC OBSERVATIONS IN MAN

*Modification of Electroencephalogram.* The human electroencephalogram does not show any alteration of its fundamental pattern following intravenous or intramuscular administration of chlorpromazine in a clinical dosage (25 to 100 mg.). This was first reported by Terzian,[28] and later confirmed by a number of other investigators.[3, 22] Terzian also reported an accentuation of the theta component and a slight increase in the amplitude of the normal rhythms. Rapid rhythms in the electroencephalogram of patients suffering from certain lesions of the brain stem disappeared after some days of treatment with chlorpromazine. On the basis of his electroencephalographic data, Terzian concluded that the sleep induced by chlorpromazine is in every way similar to, if not identical with, physiologic sleep in all its stages of depth.

Bente and Itil[29] observed no fundamental alteration of the normal electroencephalogram after chlorpromazine, but they noted a tendency toward a slowing of the tracing and demonstrated an increase of abnormal rhythms if these had been present before the administration of the drug.

*Modification of Response to Other Drugs.* All observers agree that chlorpromazine has a

pronounced potentiating effect on most cerebral depressants. Bente and Itil[29] showed that the potentiating action of chlorpromazine on the appearance of fast waves in the electroencephalogram of patients who were given evipal intravenously persisted for a few days only and could not be demonstrated after patients had been on chlorpromazine for several weeks. Until now, no agent has been described that would reliably counteract the central effects of chlorpromazine. On the basis of clinical observations, some authors have cautioned against the use of analeptics with strong excitatory action on the cortex, since they believe that these substances may produce convulsions in patients who have received chlorpromazine.[3]

*Modification of Total Behavior.* The principal central action of chlorpromazine in man consists in the marked inhibition of all spontaneous psychomotor activity. Patients under the effect of large doses of the drug are generally sluggish, often somnolent, and tend to be apathetic. In spite of their decreased alertness, they respond easily and adequately to sensory stimuli. Lehmann and Hanrahan[3] have shown that the higher psychic functions involving learning, remembering, and discrimination are not significantly impaired.

In patients with intractable pain, the drug has proven its value.[30] It seems that the pain sensation as such is not affected, but the patient's emotional reaction to it, his personal involvement with pain as a disorganizing experience, is greatly diminished.

We have observed an apparent lowering of the convulsive threshold following chlorpromazine administration that may lead to greater frequency of seizures in epileptics receiving the drug. This phenomenon may be related to one of the characteristic properties of chlorpromazine, namely, that it inhibits desynchronization of the electroencephalogram and favors its synchronization.

Clinical observations of chlorpromazine in patients with dyskinetic syndromes (hemiballismus, dystonia musculorum deformans, Sydenham's and Huntington's chorea) have established its favorable action in these conditions.[7, 8, 31, 32] In patients with paralysis agitans who presented rigidity and tremor, the rigidity was diminished after chlorpromazine was administered and the tremor was reduced from four to five per second to two to three per second, or it was completely abolished.[33]

While chlorpromazine in moderate doses reduces the symptoms of patients with parkinsonism, it may in larger cumulative doses produce an extrapyramidal syndrome that appears to be identical with parkinsonism. Patients suffering from this drug-induced parkinsonism, which is reversible and disappears within a few days after the drug has been discontinued, will respond to antiparkinsonian drugs. One may speculate that this paradoxical effect can be explained by primary inhibition of the parkinsonian tremor that originates in the reticular formation. With higher concentrations of the drug, an ascending action may be presumed that then will affect the basal ganglia and inhibit the subcortical centers responsible for associated and expressive movements, although it leaves the cortical functions comparatively intact.

## NEUROCHEMISTRY

Peruzzo and Forni[34] found that chlorpromazine depresses the cellular metabolism of brain slices, and Lindan[35] confirmed these observations by demonstrating certain differences

between the depressive effect of chlorpromazine and that of barbiturates. The former resembles the metabolic action of the latter, however, in that carbohydrate metabolism is affected only above the succinate level.

Grenell et al[36] report that chlorpromazine in rats induced a selective increase of adenosinetriphosphate. While this substance increases throughout the entire brain following chlorpromazine, its greatest increase occurs in the midbrain.

Tatlow et al[31] showed that chlorpromazine suppresses acetylcholine release from the cat's cortex, and that a similar effect is observed in the cortical tissue of schizophrenic patients removed at lobotomy.

## DISCUSSION

On the cellular level, it appears that chlorpromazine has a depressant effect on brain metabolism and a selective metabolic action in the midbrain area. On the multineuronal level, it acts as a synchronizer of cerebral electrical activity. It inhibits the activity of the reticular formation and suppresses its facilitating and desynchronizing functions. In preventing the establishment of a normal arousal reaction, chlorpromazine blocks the afferent impulses that normally reach the cortex through the collateral connections of the reticular-activating substance with the long sensory paths. The favorable effect in dyskinetic syndromes may be explained by the blocking of the efferent facilitation impulses that arise or are enhanced in the reticular-activating substance and are responsible for clinically observed involuntary movements. The lowering of the convulsive threshold of epileptic patients may depend on preventing the full development of a desynchronizing arousal reaction under the bombardment of sensory stimuli, since it is known that such desynchronizing cortical discharges can protect against seizures.

While these effects of the drug are well established through experimental evidence, two major questions remain: (1) How does chlorpromazine produce these specific effects at the cellular and multineuronal levels? (2) How can its action on the total behavior and psychic functions be explained, and what rationale can be offered for its therapeutic effects?

French investigators have referred to the pharmacologic action of chlorpromazine as "ganglioplegic" and "neuroplegic."[37] It has been shown, however, that the drug has no clear-cut ganglion-blocking property.[13] Dasgupta and Werner[38] have compared the effects of chlorpromazine with the inhibitory action of a typical "inter-neuron blocking" drug such as myanesin. They found that chlorpromazine is about 20 to 40 times more potent than myanesin, except for its action on the spinal cord activity and on motor activity resulting from stimulation of pyramidal tracts, where chlorpromazine proved to be almost ineffective. These authors conclude that chlorpromazine appears to interfere with motor activity primarily by its depressant effect on the central facilitation originating in the brain stem reticular formation.

Decourt[39] has coined the term "narcobiosis" for the universal depressant action on cellular activity that chlorpromazine exerts, according to him. He has shown that highly active cells, such as germinating seeds, are more susceptible to this narcobiotic action. When

administered in clinical dosage to mammals, the cells of the central nervous system are most significantly inhibited.

Charatan[40] regards the blocking action of chlorpromazine as unspecific, and points out that this drug is a tertiary ammonium compound and, as such, it penetrates fairly easily into nervous tissue. Longo et al[17] also draw attention to the difference between the peripheral ganglion-blocking action of the quaternary ammonium compounds and the central action of the tertiary amines, and they relate this to the difference in the relative ease of penetration of tertiary amines and quaternary salts in the central nervous system.

At this stage it is not possible to determine whether the neurophysiologic action of chlorpromazine is due to its specific affinity for cells in the reticular-activating formation, or whether it can be explained simply on the quantitative basis of a higher density of cell population in that area.

Lehmann et al[3] and Longo et al[17] draw a parallel between the observations of Himwich on the antiacetylcholine effects of various antihistaminics in the central nervous system and the central action of chlorpromazine.[41]

Any attempt to explain the effect of the drug on total behavior and psychic functions must be based on the drug's characteristic and fundamental action on the reticular-activating system. The drug produces a syndrome characterized by somnolence, lack of motor initiative, disinclination to walk, and vacuity of expression. This is precisely the syndrome described by Ingram et al[42] in cats with experimental lesions in the caudal hypothalamus and the tegmentum of the cephalic end of the midbrain. Ransom[43] in monkeys and Nauta[44] in rats obtained similar results.

We have referred to the characteristic action of chlorpromazine as "selective inhibition" because of its remarkable property of inhibiting lower functional centers of the central nervous system without significantly impairing the function of the cortex.[33] The essential difference between the action of pharmacologic agents capable of producing selective inhibition, such as chlorpromazine, and the effects of older sedatives such as the barbiturates is that ordinary sedation is nonselective. Nonselective sedatives, through their action on the cerebral cortex, tend to produce disinhibition of affect with consequent loss of emotional control and clouding of intellectual processes. The selective inhibition of chlorpromazine is manifested clinically in decreased alertness, reduced affective responsiveness, and diminished spontaneity, while the higher psychic functions anatomically represented in the cortex are not significantly affected.

Various authors have proposed a rationale for the therapeutic action of chlorpromazine in psychotic conditions. It has been repeatedly pointed out that this action is probably not curative but corrective in nature, although, like the effect of digitalis in cardiac disease and of insulin in diabetes, it is of high therapeutic value. Some authors have spoken of a "pharmacodynamic lobotomy" that interrupts the corticodiencephalic connections. Laborit thinks that the disconnection of the neurovegetative system effected by the drug is of great importance. Delay and Deniker[37] draw attention to the difference between the shock therapies used in psychiatry and the treatment with chlorpromazine. With the shock therapies, stimulation is intense and the countershock resting phase is less important, while

chlorpromazine therapy is distinguished by a mild initial shock phase followed by a very long resting phase. Staehelin,[45] referring to the fact that 30 years ago chronic schizophrenic patients who contracted encephalitis and developed parkinsonian symptoms improved considerably in their mental condition, implies a possible antagonism between the extrapyramidal hypokinetic syndrome and the schizophrenic process.

Our own speculations are based on the distinction of three functional systems in the psychophysiologic sphere: (1) visceropsychic, (2) sensorypsychic, and (3) corticopsychic.

Visceropsychic activity dependent on stimulation from the reticular-activating system to the cortex is primarily affect conscious in its orientation. Sensory-psychic activity depends on the more highly structured stimuli delivered by the long sensory paths to the cortex. It is object conscious or reality conscious in its orientation. Corticopsychic activity is maintained by internuncial systems within the cortex. It is capable of providing very highly structured stimuli, and may be regarded as chiefly concept conscious or symbol conscious in its orientation.

We assume that the individual builds his ego structure through corticopsychic evaluation and by the integration of impulses reaching the cortex from the sensory and visceropsychic systems. The structure of the ego may disintegrate under excessive bombardment from the visceropsychic system, which is responsible for the transmission and elaboration of affective reactions. By blocking the disastrous influx of impulses from the visceropsychic system, anatomically represented in the midbrain and hypothalamus, the individual can reconstruct and retest his ego defenses without danger of a catastrophic reaction.

The essentially new factor in the therapeutic approach with chlorpromazine may lie in the fact that the drug does not inhibit the corticopsychic and sensory-psychic systems, but may actually improve their functioning since it blocks only the disturbing action of excessive drive or dysphoric affect related to the activity of the visceropsychic system.

Such a theoretic model could account for the dramatic therapeutic results observed with chlorpromazine in acute psychotic breakdowns where the patient's ego may suddenly be relieved from pressure and be given a chance to reorganize its defenses. This theory could also explain the therapeutic effect of selective inhibition in chronic schizophrenics inasmuch as the relative freedom from disorganizing tensions and anxieties, achieved with maintenance chlorpromazine therapy, enables the patient to attain a new level of socialization and acculturation because he is no longer forced into autistic withdrawal as his only defense.

## SUMMARY

The principal site of action of chlorpromazine is in the central nervous system, and the most powerful impact of this drug has been felt in the field of psychiatry. The drug is therapeutically effective in a variety of acute psychotic conditions. It has also produced dramatic remissions in chronic psychotic states, and has, for the first time, introduced into psychiatry the principle of pharmacologic maintenance therapy of functional psychoses.

The systematic investigation of the neurophysiologic action of chlorpromazine has mainly depended on three methods: (1) modification of the electroencephalogram, (2) modification of responses to other drugs, and (3) modification of total behavior.

Chlorpromazine inhibits rapid potentials in the electroencephalogram, suppresses the mechanisms responsible for desynchronization of the electroencephalogram as manifested in the arousal reaction, and raises the threshold for direct electric stimulation of the reticular-activating system. In man, it tends to enhance abnormal rhythms when these are present prior to administration of the drug.

The drug has a strong potentiating effect on most cerebral depressants. It inhibits convulsions induced by nicotine through its action on chemoreceptors in the midbrain, but it is not effective against convulsants such as metrazol, picrotoxin, or strychnine, which act primarily on the cortex. In epileptic patients, it seems to lower the convulsive threshold. Its inhibitory action on chemoreceptors in the reticular-activating system is also manifested by the suppression of apomorphine-induced vomiting and the suppression of central excitation in response to adrenalin.

Chlorpromazine inhibits conditioned reflexes in animals but does not abolish unconditioned avoidance reactions. It suppresses sham rage in diencephalic cats.

The oxygen consumption of cortical slices is reduced by chlorpromazine and there is evidence of its influence on adenosinetriphosphate and acetylcholine metabolism in the brain.

In man, it produces a syndrome characterized by lack of motor initiative and a flattening of affective experience and expression. It diminishes involuntary movements due to various dyskinesias, probably through inhibition of the facilitation impulses arising in the reticular-activating system. In large doses it produces a parkinsonian-like picture in some patients, possibly because of its ascending action on the basal ganglia.

Various theories proposed for its therapeutic action are discussed, and the concept of selective inhibition is suggested for the description of the specific action of this drug that acts on lower neuronal units without significantly affecting the cortical centers. The concepts of visceropsychic, sensory-psychic, and corticopsychic systems are introduced in an attempt to interpret the therapeutic action of chlorpromazine in terms of physiodynamic as well as psychodynamic organization on which the ego depends for its undisturbed function.

RESUMEN

El sitio principal de acción de la cloropromazina es el sistema nervioso central, siendo eficaz en una variedad de procesos psicóticos agudos y produciendo remisiones espectaculares en estados psicóticos crónicos.

La cloropromazina inhibe potenciales rápidos en el EEG y elimina el mecanismo responsable de la desincronización del EEG. Tiende a mejorar los ritmos anormales en el hombre, cuando éstos existen antes de la administración del medicamento.

La cloropromazina posee un potente efecto en la mayoría de las depresiones cerebrales e inhibe las convulsiones inducidas por la nicotina, pero no es eficaz contra los agentes convulsionantes como el metrazol, picrotoxina o estricnina.

La cloropromazina produce en el hombre un síndrome caracterizado por la falta de iniciativa y "aplanamiento" de la expresión y práctica afectivas. Disminuye los movimientos involuntarios debidos a varias disquinesias. En dosis masivas produce en algunos pacientes un cuadro del tipo parkinsoniano. El autor discute las varias teorías propuestas para

explicar la acción de este medicamento y sugiere la idea de que dicha acción puede estar relacionada con tres sistemas funcionales psicofisiológicos: visceral, sensorial y corticopsíquico.


RESUME

La chlorpromazine exerce son action principalement dans le système nerveux central. Le médicament est éfficace dans une variété de conditions psychotiques aiguës, produisant des améliorations dramatiques dans des états de psychose chronique.

La chlorpromazine inhibe les potentiels rapides de l'électroencephalogram, et elle supprime le mecanisme responsable de la désynchronisation du EEG; dans l'homme, elle tend à augmenter les rythmes anormaux quand ceux-ci sont en évidence avant l'administration du médicament.

La drogue exerce une forte action de potentialisation sur la plupart des dépressifs cérébraux. Elle inhibe les convulsions induites par la nicotine, mais elle est sans effet contre les tels convulsants tels que le métrazol, la picrotoxine et la strychnine.

Chez l'homme, la chlorpromazine produit un syndrome caracterisé par un manque d'initiative moteur et un tamponnement de l'expérience et l'expression affectives. Elle diminue les movements involontaires dus à diverses dyskinésies. En forte dose, elle produit chez quelques malades des symptômes analogues à ceux de la maladie de Parkinson. L'auteur discute les différentes théories proposées pour expliquer l'action de la chlorpromazine. Il théorise que cette action peut être reliée à trois systèmes psychophysiologiques: le système viscero-psychique, le système sensorio-psychique et le système cortico-psychique.


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# 17-Hydrocorticosteroid Levels in the Peripheral Blood of Psychotic Patients under Treatment with Chlorpromazine and Reserpine

## A Preliminary Study

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In the course of studies on the level of 17, 21-dihydroxy-20-ketosteroids (17-OHCS) in the peripheral blood of psychotic patients,[1] it was decided to extend the study to patients under therapy with the ataractic medications chlorpromazine and reserpine.

### MATERIALS AND METHODS

The subjects were 24 patients under chlorpromazine medication and 27 under reserpine. All were hospitalized male psychotics residing in the same pavilion of the Continued Treatment Service, most of whom had the diagnosis of schizophrenia.

Twenty cubic centimeters of blood was drawn from the antecubital vein in a syringe wet with a film of 1 per cent solution of heparin.* The blood was centrifuged immediately, the supernatant plasma was separated from the cells, and the plasma 17-OHCS determined according to the Porter-Silber[2] method.

Except for the administration of one or the other of the tranquilizers, the patients were not subjected to any other therapeutic procedure for at least a week before blood sampling.

The "normal" control group and the two untreated psychotic groups used in our previous study[1] serve here as frames of reference.

### RESULTS

The 17-OHCS values, the dosage, and the duration of medication as well as the clinical status of the patients appear in tables I and II, for the chlorpromazine and the reserpine groups, respectively. The difference between the mean of the chlorpromazine group and the mean of the reserpine group is statistically significant well beyond the 0.001 level of probability.

In table III are summarized the data from this study and from the three series included in the previous study.[1] These five series are in turn each reclassified and subgrouped into three: (a) subjects whose values fall into the normal (10 to 25 gamma/100 ml.), (b) subnormal (1 to 10), and (c) supranormal ranges (25+ gamma/100 ml.). Over 58 per cent of the values in the chlorpromazine series are subnormal, compared with 4 per cent of those

* The trade name of Organon, Inc., for heparin is Liquaemin.

in the reserpine series. The chlorpromazine series also shows the lowest range of values of the five subgroups. These findings support the impression that chlorpromazine lowers the 17-OHCS level in the blood of these patients.

Although the fact that the reserpine series has the highest mean level (22.18 sigma 6.18) and the highest percentage of supranormal values (37 per cent), suggesting that this drug raises the level of 17-OHCS, more data will be required to confirm this probability.

## DISCUSSION

The reason for the use of the Porter-Silber method has been stated in the previous communication.[1]

It should be noted that this work is only preliminary, and the data were obtained by random sampling. No premedication levels were determined and no serial studies were performed. The doses of chlorpromazine ranged from 0.2 to 2.4 Gm. (the latter in only one instance), a spread of 12 times, and from 5 mg. orally to 15 mg. (10 mg. intramuscularly

TABLE I

*Blood 17-OHCS in 24 Psychotics under Chlorpromazine*

| Subject | Age | Diagnosis | Details of medication: Date, dosage (Gm.) | Effect of medication | Date of blood sample | 17-OHCS (gamma/100 ml.) |
|---|---|---|---|---|---|---|
| M.G. | 25 | DP, paranoid | 2/27: .075 Gm. to 4/29; 1.2 Gm. to 5/8 | i | 5/8 | 17 |
| T.J. | 48 | DP, paranoid | 2/1: 1.2 Gm. to 4/26; 8 Gm. to 5/3; .4 Gm. to 5/10 | i | 5/10 | 4 |
| W.M. | 44 | DP, paranoid | 3/4: 1.2 Gm. to 5/10 | i | 5/10 | 0 |
| R.N. | 30 | Psychosis convul. disorder | 2/25: 1.2 Gm. to 4/12; 4 Gm. to 5/10 | i | 5/10 | 3 |
| H.W. | 30 | DP, hebephrenic | 10/11: 4 Gm. to 12/16; 1.2 Gm. to 4/16; .2 Gm. to 5/10 | i | 5/10 | 3 |
| P.F. | 48 | DP, catatonic | 12/9: 1.2 Gm. to 5/10 | i | 5/10 | 0 |
| G.J. | 46 | DP, catatonic | 12/5: 1.2 Gm. to 5/10 | i | 5/10 | 11 |
| W.H. | 33 | DP, hebephrenic | 4/12: 1.2 Gm. to 4/22; .2 Gm. to 5/10 | i | 5/10 | 2 |
| O.G. | 30 | DP, paranoid | 10/11: .4 Gm. to 10/16; 1.2 Gm. to 5/10 | u | 5/10 | 14 |
| K.J. | 39 | DP, catatonic | 4/16: .8 Gm. to 5/11 | i | 5/11 | 14 |
| F. | 32 | DP, paranoid | 5/2: 1.2 Gm. to 5/11 | u | 5/11 | 2 |
| V.P. | 29 | DP, catatonic | 3/14: 1.2 Gm. to 5/4; .4 Gm. to 5/18 | i | 5/18 | 19 |
| S.A. | 24 | DP, paranoid | 5/4: 1.2 Gm. to 5/18 | u | 5/18 | 22 |
| I.A. | 24 | DP, mixed | 4/26: 1.2 Gm. to 5/18 | i | 5/18 | 13 |
| K.S. | 31 | DP, hebephrenic | 1/26: 1.2 Gm. to 3/26; 4 Gm. to 5/24 | i | 5/24 | 8 |
| P.E. | 36 | DP, catatonic | 3/24: 1.2 Gm. to 4/12; .8 Gm. to 6/1 | i | 6/1 | 22 |
| L.R. | 27 | DP, catatonic | 3/19: 1.2 Gm. to 6/1 | i | 6/1 | 17 |
| M.V. | 20 | Psychosis with mental deficiency | 5/25: 1.2 Gm. to 6/1 | i | 6/1 | 2 |
| B.J. | 28 | DP, paranoid | 6/1: 1.2 Gm. to 6/15 | i | 6/15 | 2 |
| G.D. | 45 | DP, hebephrenic | 5/26: 2.4 Gm. to 6/15 | u | 6/15 | 5 |
| R.D. | 39 | DP, catatonic | 6/9: 1.2 Gm. to 6/15 | u | 6/15 | 4 |
| C.W. | 24 | Psychosis with psychopath. person. | 6/30: 1.2 Gm. to 7/15 | u | 6/15 | 4 |
| D.G. | 31 | DP, paranoid | 5/8 to 6/1: 1.2 Gm.; .4 Gm. to 6/15 | i | 6/15 | 16 |
| J.S. | 36 | DP, paranoid | 6/12: 1.2 Gm. to 6/15 | i | 6/15 | 4 |

Key to table: DP = dementia praecox; i = improved; u = unimproved; mean = 8.52 ± 3.41 gamma/100 ml.; N = 24.

TABLE II

*Blood 17-OHCS in 27 Patients under Reserpine*

| Subject | Age | Diagnosis | Details of medication: Dates, dosages (mg.), and routes | Effect of medication | Date of blood sample | 17-OHCS (gamma/100 ml.) |
|---|---|---|---|---|---|---|
| M. | 23 | Psychosis with mental deficiency | 4/22: 10 I.M. and 5 p.o. to 5/1; 5 p.o. to 5/5 | u | 5/5 | 19 |
| W. | 20 | DP, hebephrenic | 1/14: 10 I.M. and 5 p.o. to 3/1; 3 p.o. to 5/5 | i | 5/5 | 26 |
| A. | 42 | DP, catatonic | 12/16: 10 I.M. and 5 p.o. to 2/1; 5 p.o. to 5/5 | i | 5/5 | 27 |
| M2 | 33 | DP, catatonic | 12/16: 10 I.M. and 5 p.o. to 5/5 | i | 5/5 | 19 |
| B. | 36 | DP, paranoid | 1/7: 10 I.M. and 5 p.o. to 3/1; 2 p.o. to 5/5 | i | 5/5 | 8 |
| R. | 40 | DP, paranoid | 1/5: 10 I.M. and 5 p.o. to 2/1; 20 and 5 to 5/5 | u | 5/5 | 12 |
| T. | 31 | Undiagnosed psychosis | 12/9: 10 I.M. and 5 p.o. to 5/5 | u | 5/5 | 25 |
| W2 | 29 | DP, catatonic | 1/7: 10 I.M. and 5 p.o. to 4/1; 5 p.o. to 5/5 | i | 5/5 | 32 |
| R2 | 47 | DP, paranoid | 1/17: 10 I.M. and 5 p.o. to 2/1; 20 and 5 to 4/1; 5 p.o. to 5/5 | i | 5/5 | 21 |
| C. | 47 | DP, paranoid | 4/26: 10 I.M. and 5 p.o. to 5/8 | u | 5/8 | 27 |
| H. | 63 | Manic dep. manic | 1/16: 10 I.M. and 5 p.o. to 3/1; 4 p.o. to 4/26; 5 p.o. to 5/8 | i | 5/8 | 30 |
| M3 | 35 | DP, paranoid | 4/18: 10 I.M. and 5 p.o. to 5/8 | u | 5/8 | 23 |
| A2 | 74 | Psychosis with cerebral arterioscl. | 4/9: 5 p.o. to 5/8 | i | 5/8 | 21 |
| M4 | 28 | DP, paranoid | 2/23: 10 I.M. and 5 p.o. to 5/1; 3 p.o. to 5/8 | u | 5/8 | 20 |
| T2 | 42 | DP, catatonic | 1/31: 10 I.M. and 5 p.o. to 3/29; 3 p.o. to 5/1; 10 p.o. to 5/8 | u | 5/8 | 42 |
| B2 | 52 | DP, paranoid | 4/12: 10 I.M. and 5 p.o. to 5/8 | i | 5/8 | 28 |
| T3 | 49 | Manic dep. mixed | 5/4: 10 I.M. and 5 p.o. to 5/11 | i | 5/11 | 14 |
| M5 | 18 | DP, catatonic | 4/18: 5 I.M. and 3 p.o. to 5/11 | u | 5/11 | 22 |
| W3 | 25 | DP, paranoid | 4/12: 10 I.M. and 5 p.o. to 5/11 | i | 5/11 | 12 |
| S. | 30 | DP, catatonic | 1/31: 10 I.M. and 5 p.o. to 5/18; 5 p.o. to 5/24 | u | 5/24 | 32 |
| V. | 33 | DP, catatonic | 1/11: 10 I.M. and 5 p.o. to 4/5 | i | 5/24 | 21 |
| L. | 72 | Manic dep. manic | 3/23: 10 I.M. and 5 p.o. to 4/21; then from 5/15 to 5/24 | i | 5/24 | 16 |
| Y. | 50 | DP, hebephrenic | 1/24: 10 I.M. and 5 p.o. to 4/6; 10 p.o. to 5/24 | i | 5/24 | 26 |
| C2 | 31 | DP, catatonic | 1/22: 10 I.M. and 5 p.o. to 4/2; 5 p.o. to 5/16; 5 I.M. and 10 p.o. to 5/24 | u | 5/24 | 24 |
| Y2 | 59 | Invol. psychosis | 5/5: 5 I.M. and 10 p.o. to 5/18; 10 I.M. and 5 p.o. to 5/24 | i | 5/24 | 11 |
| G. | 18 | DP, undif. | 5/17: 10 I.M. and 10 p.o. to 6/1 | u | 6/1 | 35 |
| W4 | 20 | DP, undif. | 5/20: 10 I.M. and 5 p.o. to 6/1 | i | 6/1 | 23 |

Key to table: DP = dementia praecox; I.M. = intramuscular; p.o. = oral; i = improved; u = unimproved; N = 27; mean = 22.18; sigma = 6.18.

TABLE III

*Distribution of Values in Subgroups According to Normal Limits*

| Groups | Number of subjects | 17-OHCS (gamma/100 ml.) Range | Mean | Sigma | Subgroups (gamma/100 ml.) 0–10 No. | % | 10–25 No. | % | 25+ No. | % |
|---|---|---|---|---|---|---|---|---|---|---|
| "Normal" control | 26 | 3–34 | 18 | 7.33 | 3 | 12 | 20 | 77 | 3 | 12 |
| Untreated "agitated" psychotics | 21 | 0–49 | 17.2 | 12.07 | 5 | 24 | 14 | 67 | 2 | 10 |
| Untreated "deteriorated" psychotics | 21 | 0–41 | 16.71 | 11.17 | 6 | 29 | 9 | 43 | 6 | 29 |
| Chlorpromazine | 24 | 0–22 | 8.52 | 3.41 | 14 | 58 | 10 | 42 | 0 | 0 |
| Reserpine | 27 | 8–42 | 22.18 | 6.18 | 1 | 4 | 16 | 59 | 10 | 37 |

and 5 mg. orally) for reserpine, a spread of 3 times. Nor was the duration of medication prior to blood sampling constant, being 3 to 211 days for chlorpromazine and 7 to 137 days for reserpine.

In spite of the randomness of the study and variations in drug administration, the values indicate that chlorpromazine lowers the 17-OHCS level and suggest that reserpine either does not affect the level or raises it. The observation on chlorpromazine finds support in the work of Chemoyl et al[3] showing that this drug given to rats subjected to stress prevents the reduction of adrenocortical ascorbic acid.

The data available from this preliminary work do not warrant an attempt to correlate the 17-OHCS level with the degree of clinical improvement. Such a task must be left for future studies involving a larger number of patients and with more refined experimental design.

These preliminary findings warrant a more controlled study of the endocrine physiology of these two important ataractics.

SUMMARY

In a study of the levels of 17, 21-dihydroxy-20-ketosteroids in the peripheral blood of psychotic patients under treatment with chlorpromazine (group I) and with reserpine (group II), it was found that group I showed significantly lower values while group II showed suggestively higher values than in unmedicated psychotics and in normals.

ACKNOWLEDGMENT

The authors would like to acknowledge the nursing assistance of E. Jacobi and F. Pindiak and the nursing staffs, and the statistical assistance of S. R. Graham and M. L. Rawn. Special thanks are due Dr. Robert H. Silber for his unfailing assistance. We also wish to acknowledge the generosity of Smith, Kline & French and of Ciba for supplying, respectively, the chlorpromazine and the reserpine.

RESUMEN

En un estudio de las concentraciones de 17, 21-dihidroxi-20-cetosteroides en la sangre

periférica de pacientes psicóticos tratados con cloropromazina (grupo I) y con reserpina (grupo II), se halló que el grupo I presentaba valores significativamente más bajos, mientras que en el grupo II los valores eran notablemente más altos que en los psicóticos o individuos no tratados.

RESUME

Dans une étude des niveaux des 17, 21-dihydroxy-20 cetosteroïdes, dans le sang périphérique de malades psychosés sous traitement avec la chlorpromazine (groupe I) et avec la réserpine (groupe II), il fut constaté que le premier groupe montrait des valeurs sensiblement plus basses, tandis que le deuxième groupe avait des valeurs sensiblement plus élevées que celles des sujets psychotiques sous médication ou des normaux.

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## *Antibiotic Medicine* Expanded to Include Clinical Therapy

With the June issue, the name of the journal, Antibiotic Medicine, will be changed to Antibiotic Medicine & Clinical Therapy, according to a recent announcement by the editors, Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D. The scope of AM&CT will be enlarged to include, in addition to the present material on the clinical use of antibiotics, original papers, abstracts, news, and advanced reports on the clinical use of all chemotherapeutic agents, such as the sulfonamides, vitamins, hormones, tranquilizers, and others.

The Editors are honored to announce that Albert H. Holland, M.D., Medical Director of the Food and Drug Administration, will join AM&CT as Consulting Editor in charge of the new section on Clinical Therapy. Formerly, Dr. Holland was Medical Director of the Armour Laboratories in Chicago, and prior to that he was Director of the Office of Research and Medicine at the Oak Ridge (Tenn.) Operations of the Atomic Energy Commission.

Antibiotic Medicine & Clinical Therapy, a monthly, is one of the seven journals published by MD Publications, Inc.

# Some Interesting Pharmacodynamic Properties of Chlorpromazine

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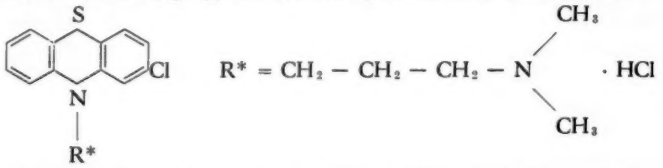
For many years the amine derivatives of phenothiazine have been studied by French researchers because of their effects, primarily antihistaminic and antiparkinsonian and, secondarily, sedative. In 1950, Charpentier, searching for a phenothiazine compound with more marked central nervous system depressant qualities than existing drugs, synthesized chlorpromazine, 10-(3-dimethylpropylamine)-2-chlorphenothiazine hydrochloride.




Numerous investigators subsequently uncovered a wide range of properties associated with this agent; at the moment chlorpromazine would appear to possess a range of activity approaching that of the adrenal corticoids. The drug was found useful in combating the nausea and vomiting of diverse etiologies; some reported on its value in potentiating narcotics for the palliative treatment of malignant disease; it aided alcoholics in their separation from habit; chlorpromazine was used in hypothermia and as an adjunct to anesthetic premedication; and, lastly, perhaps its widest use to date is in the general field of psychiatry.

Early in the course of study of this compound, the ability to depress the autonomic system was believed to be the result of a ganglionic-blocking property for which the French termed chlorpromazine a "ganglioplegic." The classic test for a ganglionic-blocking agent is the ability of a drug to prevent contraction of the nictitating membrance of a cat preparation when the corresponding preganglionic fibers have been stimulated. In this type of experiment the chemical mediator at the effector cell is epinephrine (adrenalin). Chlorpromazine, however, is capable of reversing the characteristic actions of epinephrine; this has been termed its "adrenolytic property," and hence erroneous conclusions have been drawn with regard to its action on the autonomic ganglion. In a series of unpublished studies,[1] animals were premedicated with 1 mg./Kg. of chlorpromazine; not only was the response to preganglionic stimulation of the fibers to the nictiating membrane absent, but also the response to direct postganglionic stimulation was not obtained.

## PHARMACODYNAMIC EXPERIMENTS AND RESULTS

In figure 1A, the normal hypertensive response to exogenous adrenalin in the laboratory animal is seen. The animal was anesthetized with pentobarbital, and its adrenals were

tied off to eliminate this possible complicating source of adrenalin. Following the injection of chlorpromazine, two changes can be seen in the carotid systolic pressure of the animal (figure 1D). First, there is a lowering of the baseline pressure, and, secondly, the hypertensive effect of the adrenalin has not only been depressed, but it has also been reversed. This is an example of the "adrenolytic effect" often alluded to in discussions of this compound.

In figures 1B, 1E, and 1F, it can be seen that there is no decrease in activity of 1,1-dimethyl-4-phenylpiperazinium (DMPP) following the injection of chlorpromazine. DMPP is a very potent autonomic ganglion stimulant that can be blocked by tetraethylammonium chloride (TEAC) and hexamethonium ($C_6$). The blockade of smaller doses of DMPP (figures 1B and 1E) is probably caused by the peripheral adrenolytic action of chlorpromazine. This further substantiates the fact that chlorpromazine is not an autonomic ganglion-blocking agent. The hypotensive effect of furfuryl trimethyl ammonium iodide, a parasympathetic agent,[3] (figure 1A) appears relatively enhanced in the absence of compensatory vasoconstriction (figure 1F) following chlorpromazine.

Decourt[1] compared the ability of hexamethonium and chlorpromazine to suppress salivary secretion when the corresponding preganglionic fibers were stimulated. In this experiment the chemical mediator is acetylcholine, thus eliminating the adrenolytic effect of chlorpromazine from this study. Therapeutic doses of hexamethonium blocked the salivary response to stimulation; chlorpromazine was only partially effective and then only in doses exceeding the usual therapeutic range. Large doses of chlorpromazine exhibit some anticholinergic properties,[4] thus explaining the partial effectiveness of this drug in depressing salivary response. In figures 1C, 1E, and 1F, comparison of the response to peripheral vagal stimulation indicates that the intensity of the pressure fall is modified by the anticholinergic action of chlorpromazine, but only after larger than normal doses.

## DISCUSSION

The peripheral adrenolytic effects of chlorpromazine account for only a small portion of its many actions. The influence of this drug on the central nervous system appears to be responsible for the major portion of its laboratory and clinical manifestations. At present there is no agreement as to a single focus of action in the central nervous system, although the areas proposed are interconnected. The hypothalamus is believed by some[5] to be the target site in the central nervous system, while others[6, 7] postulate that the ascending reticular-activating system is the site in the central nervous system that is dominated by chlorpromazine.

The regulation of numerous vital functions has been assigned to the hypothalamus.[8] In addition to the control of fat and carbohydrate metabolism, this region of the diencephalon is concerned with temperature regulation and the sleep processes. The posterior collection of nuclei within the hypothalamus governs sympathetic activity, while the anterior collection is responsible for parasympathetic functions. Electrical stimulation of the posterior cell group produces dilatation of the pupils, sweating, inhibition of intestinal activity, liberation of adrenalin, and a rise in blood pressure. Stimulation of this region causes the appearance

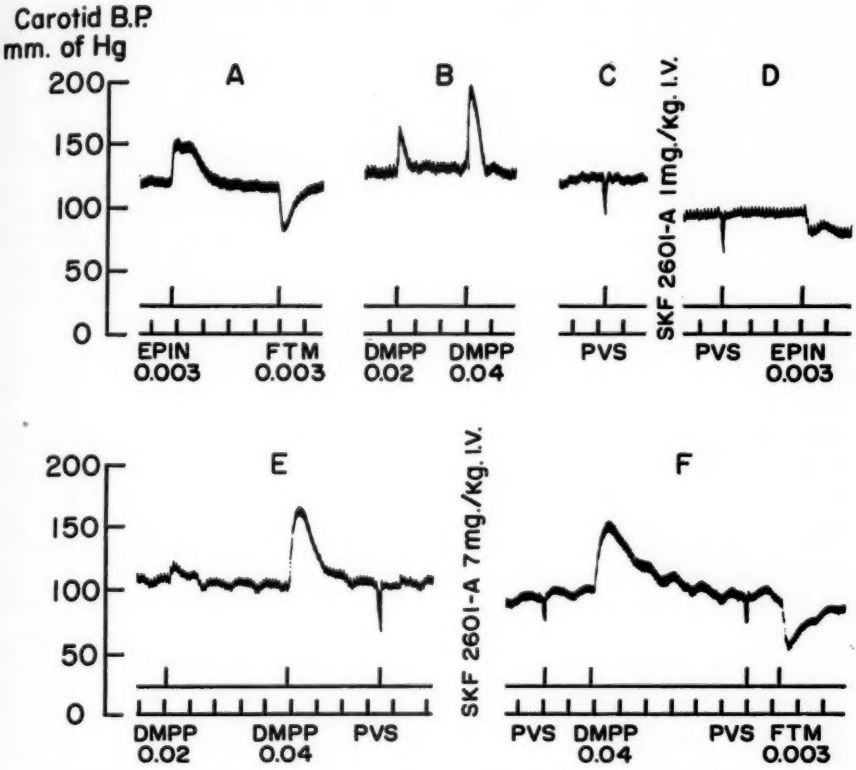



FIG. 1A, B, C, D, E, and F. Cat—adrenals tied off—pentobarbital anesthesia. Peripheral vagal stimulation (PVS) = 6 volts, 50 cycles/second, 8 seconds, right vagus. Doses in mg./Kg., IV. Time in minutes. Epin = epinephrine; DMPP = 1,1-dimethyl-4-phenylpiperazinium iodide; FTM = furfuryl trimethyl ammonium iodide; SKF 2601-A = chlorpromazine.

of extrasystoles in the laboratory animal. Depression of this area, as by a destructive lesion, prevents the occurrence of chloroform-induced arrhythmias. Other investigators have induced alterations in temperature control and a state of somnolence indistinguishable from sleep by lesions in the posterior nuclear group.

The anterior collection of nuclei within the hypothalamus appears more resistant to manipulations than the sympathetic group. This would appear to be in agreement with nature's doctrine of self-preservation, for an animal devoid of its sympathetic system can continue to survive in a protected environment, while destruction of the parasympathetic system is not compatible with life.

Anatomic relationship has been demonstrated between the prefrontal region and the

hypothalamus by means of fiber tracts to the dorsomedial nucleus of the thalamus and perhaps even by direct connections. The prefrontal cortex has been proposed as the projection area for the hypothalamus.[8] The functional relationship of these areas is undoubtedly well understood in the field of psychiatry and is beyond the scope of this discussion. After consideration of the material presented thus far, it would seem that an agent capable of depressing the hypothalamus could reproduce the various pharmacodynamic actions ascribed to chlorpromazine.

On the other hand, the neurophysiology of the ascending reticular-activating system has been carefully investigated by Magoun and his co-workers.[9, 10] The reticular formation is a multineuronal network occupying the medial portion of the brain stem from the lower level of the pons to the ventromedial area of the thalamus. Connections between the thalamic nuclei and the frontal and frontoparietal cortex have been demonstrated; the possible relationship between these regions and the hypothalamus has been mentioned previously.

By means of electrical techniques, it has been established that the ascending reticular-activating system is a multisynaptic common transport system for all modalities; collaterals are given off to this medially situated formation from the classic lateral ascending sensory pathways. A single sensory impulse is thus distributed to wide areas of the cortex. Bilateral interruption of the lateral pathways in the laboratory animal does not interfere with the receipt of peripheral stimuli or with the normal pattern of sleep and wakefulness as noted on an electroencephalogram, provided that the reticular formation remains intact. When the classic tracts are allowed to remain intact and the reticular formation is interrupted, a state of somnolence ensues and persists. Peripheral stimuli will still elicit some cortical activity, but the intensity and chronicity of the stimulation must be in excess of controls to evoke a response. Cessation of the stimulation causes the animal to revert quickly to a sleep pattern as determined by electroencephalographic tracings. The persistence of cortical activity after withdrawal of any stimulus is the result of reverberation in the intact reticular system because of its multisynaptic architecture. A summary of the experimental evidence[9, 10] indicates that the function of the reticular formation is in relation to the maintenance of a state of generalized awareness at the cortical level regarding incoming stimuli, regardless of source. It is the function of the classic sensory pathways to direct a stimulus to its specific cortical receptive area for purposes of discrimination. Expressed in simpler terms, the reticular system primes the entire cortex, while the lateral pathways fire a specific cortical area. In the absence of priming (interruption of the reticular formation), firing of the cortex (intact classic sensory pathways) is ineffective.

Peripheral sympathetic activity and circulating adrenalin also contribute to the perpetuation of the wakefulness state of an animal as a function of its response to external stresses. This cortical response is not simply a circulatory phenomenon (adrenalin acting directly at the cortex), but it is mediated by way of the reticular formation, for if the brain stem cephalad to the corpora quadrigemina is severed in the laboratory animal, the cerebral circulation remaining intact, neither peripheral sympathetic discharge nor circulating adrenalin will now evoke a cortical response. Hiebel and his co-workers[8] have shown a

blunting of cortical response to auditory and olfactory stimulation in the laboratory animal premedicated with chlorpromazine. In addition, direct electrical stimulation of the reticular formation results in a decrease in cortical as well as peripheral sympathetic discharge, as compared to control studies done with the animals that had received chlorpromazine. The significance of Hiebel's work is the fact that animals with intact reticular systems behaved much as if the reticular formation had been interrupted when the animals had been premedicated with chlorpromazine. Briefly then, we have mentioned the ascending reticular formation as being a multisynaptic medial brain-stem structure responsible for priming the cortex to the receipt of incoming stimuli of all modalities. The reticular formation is under humoral (adrenalin) as well as neural influences. Since chlorpromazine is capable of depressing the reticular formation both directly and by its adrenolytic action, some investigators postulate the ascending reticular-activating system as the most likely central nervous system site of action of this interesting compound.

SUMMARY

The peripheral adrenolytic effect of chlorpromazine has been discussed, and laboratory data have been presented to demonstrate this phenomenon.

The classification of this compound as a ganglioplegic by French researchers is inaccurate. Chlorpromazine has been shown to possess no ganglion-blocking action.

Some degree of anticholinergic activity in doses considered beyond the therapeutic range has been inferred.

At present, there seem to be two schools of thought regarding the central nervous system site of action of this drug. The hypothalamus appears to be a very interesting possibility. On the other hand, recent neurophysiologic research has suggested the ascending reticular-activating system as a target area for chlorpromazine.

ACKNOWLEDGMENT

The authors wish to thank Mr. J. F. Buckley and his associates at Smith, Kline and French Laboratories for supplies of chlorpromazine.

RESUMEN

Se ha discutido el efecto adrenolítico periférico de la cloropromazina y se han presentado los datos de laboratorio para explicar este fenómeno.

La clasificación de este compuesto como agente ganglioplégico hecho por investigadores franceses, es inexacta. La cloropromazina ha venido demostrando que no posee acción bloqueadora de los ganglios. Se ha inferido que tiene cierta actividad anticolinérgica en dosis consideradas fuera de los límites terapéuticos.

En la actualidad, parece que existen dos interpretaciones distintas en cuanto al lugar de acción de esta droga en el sistema nervioso central. El hipotálamo parece constituir una posibilidad interesante. Por otra parte, recientes investigaciones neurofisiológicas han

sugerido el sistema reticular-activo ascendente como el área sobre la cual actuaría la cloropromazina.

RESUME

L'effet adrénolytique de la chlorpromazine à la périphérie est discuté et des données de laboratoire pour démontrer ce phénomène ont été presentés.

La classification de ce composé comme un ganglioplégique par les chercheurs français est inexacte. Il a été démontré que la chlorpromazine ne possède aucune action ganglioplégique.

Avec des doses considerées comme dépassant les taux thérapeutiques, il a été inféré que le médicament possède un certain degré d'activité anticholinergique.

A présent, il paraît y avoir deux écoles concernant le site dans le système nerveux central où l'action de cette drogue peut se faire sentir. L'hypothalamus semble être une possibilité très intéressante. D'autre part, des recherches névro-physiologiques récentes suggèrent que la chlorpromazine peut exercer une action sur le système réticulaire ascendant.

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# Undesirable Effects and Clinical Toxicity of Chlorpromazine

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Although reporting of the therapeutic properties of chlorpromazine has been unusually extensive, there has been comparatively little systematic investigation of its toxicity in man. It is a remarkable fact that even though a bibliography of over 3000 papers has accumulated since its synthesis in 1950, its safety as a clinically useful drug is still debated. The consensus seems to be that although chlorpromazine possesses many undesirable side effects and occasionally produces serious complications, it is in general a safe drug that can be utilized without undue risk. It should be recognized that these conclusions have generally been based on clinical experience. On the other hand, the relatively few laboratory studies have produced no unanimous or unqualified conclusions.

Several factors indicate that an early answer to the problem should not be expected. The side effects and complications are multiple and extremely diverse in character and site of origin. They occur in widely distributed and apparently dissociated organ systems, so that each may require individual investigation. Many of the reactions are unique, and do not fulfill the etiologic criteria previously established for reactions of similar clinical appearance. Some untoward effects occur infrequently and may escape recognition as being due to chlorpromazine, as was illustrated in the case of jaundice that was not recognized until 1954 even though chlorpromazine had been subjected to extensive clinical trial in Europe for nearly two years. Finally, our limited knowledge of neurophysiology and neurochemistry, inaccessibility of the brain, and ignorance of the biologic mechanisms that may be involved in the production of mental illness are basic factors that will preclude early understanding of many of the unusual responses that may be induced by this drug.

The side effects and complications of chlorpromazine are characterized by such a high degree of unpredictability that reliable correlations have been possible only within narrow limits. The following appear to be the most consistent: (1) the majority of the side effects occur during the first two weeks of administration; (2) most of the complications appear within the second two weeks; (3) side effects tend to be more intense during intramuscular administration and when oral dosages are high. With few exceptions, side effects resolve despite uninterrupted administration. This characteristic spontaneous resolution during treatment also applies to the dermatologic complications and may be true in the case of jaundice and parkinsonism. An important feature of the complications is that they usually do not recur on subsequent administration.

Most of the undesirable effects of chlorpromazine may be attributed to action on various

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levels of the nervous system. Those that occur most frequently are central depressant, sympatholytic, parasympatholytic, and myatonic effects. Others suggest interference with the metabolic and endocrinologic aspects of hypothalamic function and disorganization of extrapyramidal motor regulation. Occurring less frequently are those complications believed to be due to allergic sensitivity. The validity of this concept is less disputed in relation to responses occurring in the skin and bronchi than it is when the liver and hemopoietic systems are involved. A third group of undesirable effects, including such diverse effects as excessive dreaming and depersonalization, defy explanation.

*Central Nervous System Effects.* The central side effects reflect more clearly than any others the possible loci of action of chlorpromazine. In general, those that occur earliest can be ascribed to a depression of the alerting function of the reticular activating system, while the later effects mostly indicate disturbed hypothalamic function and basal ganglionic release.

Drowsiness and hypersomnolence are the most common central side effects and, in fact, occur in a majority of patients receiving chlorpromazine. In rare instances, particularly in hypochondriacal or phobic patients, insomnia may be produced, but this is doubtfully a primary effect of the drug. Sedation is maximal during the first 7 to 10 days of treatment. The degree is based on dosage, route of administration, and individual sensitivity. Intramuscular injections of 50 to 100 mg. ordinarily induce sleep of from two to six hours. Oral dosages exceeding 75 mg./day may produce mild lethargy; when the dose exceeds 200 mg./day, most patients experience a nagging desire for sleep or actual hypersomnia. The patient can be awakened easily, and the perceptive and intellectual fogging so characteristic of barbiturates or other cortical depressants is minimal. If the patient cannot be aroused, other factors are present. While this potent sedative property is an effective instrument in the management of highly disturbed patients, it is troublesome and often distressing to the ambulatory patient. Fortunately it disappears rapidly, but may be protracted in those patients who must continue on very high dosage regimens.

Apathy, lack of initiative, and loss of interest in surroundings are a common response in patients receiving intramuscular doses exclusively and when the oral dosage is in the range of 600 to 800 mg. daily or higher. Affective disturbances of this quality seem to occur predominantly in previously agitated psychotic patients. Contrariwise, Hoch[19] has observed restlessness and tension accompanied by feelings of depersonalization occurring after 7 to 10 days of treatment when the dose was but 100 to 200 mg. daily. Chlorpromazine also appears to be capable of worsening depressions and perhaps even of mobilizing incipient cases. Statistics supporting this observation are lacking, but in the author's experience the incidence is sufficiently impressive to contraindicate its use in this illness.

Errors in thermoregulation, endocrinologic and metabolic changes, and other untoward effects attributable to hypothalamic dysfunction may take place at any stage of treatment, but are generally seen during the later phases, particularly if dosage is high. In our experience, the most frequent disturbance in temperature control has been in the direction of fever, usually in the form of isolated spikes of from 101 to 103 F. Subnormal temperatures, never lower than 97 F., have been uncommon, contrary to numerous reports in the European

literature describing the hypothermic capacity of chlorpromazine. Various manifestations of disordered water, fat, and carbohydrate metabolism have been reported. Courvoisier et al[13] found that chlorpromazine raised the blood sugar level in animals, and glycosuria[18, 21] has been observed clinically. However, we have been unable to detect any significant changes of this type. For purposes of this paper, aberrations in water and fat metabolism and endocrinologic function are described in other sections.

Other undesirable central effects are excessive dreaming, blurring of vision due to paresis of accommodation, and predisposition to convulsive seizures.[1, 26]

The signs and symptoms described above may be regarded as undesirable side effects, to be anticipated in a considerable percentage of patients. They are of clinical importance mainly because they are capable of causing subjective distress. In most cases they disappear rapidly despite continued administration, and the patient can be reassured to this extent. However, there are two central nervous system reactions that are of the proportions of complications and may require either reduction of dosage or interruption of therapy. They are the extrapyramidal syndromes and delirium.

Minor signs referable to the basal ganglia occur in approximately 20 per cent of patients receiving high dosages. These include sensations of restriction of movement, transient difficulties in swallowing and talking, and feelings of the tongue falling backward or that the head "wants to fly backward." Objectively there may be tremor of a static or tension type and moderate loss of associated movements. During the first two weeks of treatment many patients show a reduction in mimetic expression, which is almost masklike. Whether this is the result of apathy, a part of generalized reduction in muscular tone, a posterior hypothalamic effect similar to that which can be experimentally induced in animals by surgical lesions,[24] or of extrapyramidal origin is disputed. These various signs and symptoms are in most cases isolated findings that do not progress. In approximately 4 to 5 per cent of patients, however, there develops a picture of parkinsonism, most frequently of a postencephalitic character. Rigidity is usually more marked than tremor, sialorrhea and seborrhea are common, and there are stooped posture, masklike facies, and loss of associated movements. The dosage in most of these cases is more than 500 to 600 mg./day. If it is reduced or the drug is withdrawn, the syndrome ordinarily resolves without apparent residue within two weeks. Various antiparkinsonism agents have been used effectively. Spontaneous resolution in patients in whom the drug was not discontinued has been described.[2, 18]

Tonic spasms of various muscle groups have occurred in 2 patients in a series of 1400 cases studied at the University of Texas Medical Branch Hospitals.[9] Both patients exhibited torticollis, opisthotonos, and ticlike movements. In 1 there were also torsion spasms, reproducing the picture of dystonia musculorum deformans.

A 14 year old catatonic schizophrenic girl who had received intramuscular injections of 25 mg. of chlorpromazine for four days suddenly developed ticlike twitching of the face and arching of the back. The opisthotonic posture was intermittent and was accompanied by conjugate deviation of the head and eyes to one side. The syndrome disappeared within 18 hours after chlorpromazine was discontinued.

A 38 year old woman who had received four intramuscular injections of chlorpromazine but who had previ-

ously received high oral doses without incident suddenly developed hyperextension of the back, conjugate deviation of the head and eyes to the right, choreiform twitching of the fingers and right mouth angle, and torsion movements of the trunk to the right. Neurologic examination revealed hyperreflexia. Dismissed as being of hysterical origin, it recurred intermittently within the next four hours. Later the patient became slightly cyanotic and complained of dysphagia, and a positive Chvostek's sign was elicited. Calcium level, however, was normal. Injections of phenobarbital and calcium gluconate terminated the episode. Subsequent investigation failed to show any organic neurologic disease.

A case similar to the latter has been photographically recorded by Ayd.[3] In 1954, Labhardt[24] described torticollis and torsion movements (*arc en cercle*) occurring in patients receiving chlorpromazine, but he regarded them as psychogenic complications of an hysterical nature.

Toxic states ranging from mild confusion to typical toxic delirium are rare complications of chlorpromazine therapy. Kinross-Wright[22] has reported death in 1 patient during a toxic confusional state, with post-mortem findings of changes in the subthalamic body, globus pallidus, and hypothalamus. Confusion of this type must be differentiated from the exaggeration of existing sensorium defects that may occur in cerebral arteriosclerotic patients receiving chlorpromazine. In the latter case it is on an ischemic basis, and is due to cerebral vascular hypotension to which the aged patient is more susceptible.

*Cardiovascular Effects.* Interference with orthostatic control of blood pressure, transient arterial hypotension, and signs of peripheral vascular insufficiency are the principal untoward effects referable to the cardiovascular system. These manifestations reflect the potent sympatholytic and adrenolytic properties of this drug. As in the case of other blocking agents of this type, the action is on the peripheral vascular network[17] rather than on the myocardium. A peripheral vasodilatation is produced; cardiac responses are compensatory. Tachycardia, for example, occurs very frequently, particularly in situations requiring rapid cardiovascular readjustments, such as change of position.

Temporary reduction in recumbent blood pressure may occur after either oral or parenteral administration of chlorpromazine. A transient arterial hypotension nearly always follows intramuscular injection, particularly when the dose is 50 mg. or higher. This finding is most prominent in elderly patients and those displaying functional hypertension during intense motor activity or in whom hypertension exists for other reasons. In these cases the drop may be precipitous and of such degree that shock would ordinarily be expected, the systolic pressure falling as much as 50 to 60 mm. and the diastolic 20 to 30 mm. However, measures to counteract shock are rarely required despite what appears to be an alarming picture. This margin of safety is probably based on chlorpromazine's capacity to reverse hypertension due to epinephrine while allowing minimal sympathetic activity to be maintained by norepinephrine.[27] Cases of serious circulatory collapse, even in normotensive patients, and protracted tachycardia have occurred, and death[15, 35] has been reported, but successful termination is the rule. In the absence of complicating factors such as hypertension, the decrease in recumbent blood pressure is usually so small and short-lived as to be clinically insignificant, especially if oral administration is used exclusively. However, evidence of adrenergic blockade continues in the form of orthostatic hypotension for about the first 7 to 10 days of treatment. Approximately 50 per cent of patients receiving dosages

greater than 150 mg./day experience dizziness on postural change and exertion, simultaneous visual blurring, momentary imbalance, and occasionally syncope. These effects are greatest in cerebral arteriosclerotics in whom there may also be intensification of sensorial clouding. In a few middle-aged and elderly patients, ankle edema without evidence of cardiac decompensation has occurred.

Facial pallor commonly occurs when parenteral and high oral doses are used, but usually does not persist for longer than the first week of treatment.

*Gastrointestinal Effects.* The most widely discussed complication of chlorpromazine therapy has been jaundice. The weight of evidence now available favors the concept that the process is a reversible reaction that confines itself to temporary occlusion of the biliary canaliculi and spares the parenchyma. However, the mechanism by which it is produced is a subject of great speculation. There is no convincing evidence that chlorpromazine is a specific hepatotoxin, capable of producing liver damage in the manner of, for example, yellow phosphorus. Patients who do not develop jaundice show no disturbance in bile excretion or cellular function. Prolonged administration or large dosages do not increase the incidence or induce laboratory signs of liver damage. We have been unable to confirm the observation of Moyer et al[30] that patients with pre-existing liver pathology have an exaggerated clinical response to chlorpromazine, an observation that led to his conclusion that biotransformation of chlorpromazine may take place in the liver. Pelner and Waldman[32] postulate that chlorpromazine may act as a biologic antagonist to choline. This theory is based, however, on the highly questionable assumption that chlorpromazine causes jaundice only in poorly nourished patients. Movitt et al[29] suggest that cholestasis may be secondary to hepatic cell injury preventing normal bile hydration.

Strong presumptive evidence exists that chlorpromazine-induced jaundice is an allergic reaction that occurs in sensitive patients. In support of this concept are: (1) the relative rarity despite widespread use; (2) experiments showing that chlorpromazine is not hepatotoxic;[10] (3) occurrence on either small or large dosages after a relatively constant incubation period; (4) an unusual antigenic capacity as reflected in the frequent occurrence of other complications more closely resembling classic allergic reactions; (5) frequent histories of previous allergic reactions; and (6) a chemical structure commonly found in sensitizing drugs. Whether jaundice results from a previously existing sensitivity or develops when the patient becomes sensitized remains to be determined. The clinical course is unique and parallels that of the skin reactions: it rarely recurs on reinstitution of the drug and may even disappear without interruption of treatment.[4]

The incidence is approximately 1.4 per cent.[16] It is unrelated to dosage or route of administration. A review of fourteen reports[6, 8, 10, 20, 21, 23, 25, 28, 29, 32, 37, 40–42] in the literature reveals that of a total of 28 cases, 65 per cent were aged 40 or above, and 65 per cent were women. The clinical course is generally mild. Usually a fever occurs suddenly two or three weeks after the beginning of treatment, followed shortly by nausea or perhaps vomiting, vague abdominal pain, acholic stools, and the appearance of icterus within one to five days. Pruritus may be intense. Subjective distress is ordinarily minimal unless the patient is aroused by the physician's anxiety over the implications of liver involvement or laparotomy

is performed. Symptoms disappear within a few days and icterus clears in from two to three weeks. Variations may occur. The incubation period may be shorter or longer than two or three weeks, but does not generally extend past one month. Treatment may be terminated and jaundice appear after a latent period. It may also remain subclinical, manifesting nothing but sudden fever and characteristic laboratory findings. Icterus may be persistent; the patient of Azima and Ogle[5] was icteric for seven months. Laboratory findings are those characteristic of obstructive jaundice: hyperbilirubinemia, elevated serum alkaline phosphatase, bilirubinuria, and negative hepatocellular function tests. Biopsy studies almost routinely reveal bile thrombi in the canaliculi, varying degrees of inflammatory cell infiltration, and preservation of cell architecture. Following recovery, signs of liver damage are not discernible.

Other undesirable effects referable to the gastrointestinal tract occur frequently but are of small consequence. The most common is constipation, which usually occurs when the dosage exceeds 100 mg. daily. Unusual increases in appetite and excessive weight gain beyond that expected with relief of anxiety are often seen. This response begins during the second to fourth week of treatment and is probably a diencephalic effect. Anorexia, vomiting, and diarrhea may also occur. Pyrosis, localized substernally or in the epigastrium, may follow oral ingestion. The mechanism is difficult to understand, for chlorpromazine depresses hydrochloric acid secretion; local irritation is a doubtful explanation since the symptom tends to occur in the same patient but irregularly.

*Dermatologic Effects.* Of all the untoward effects of chlorpromazine classed as complications, dermatoses are the most common. Like so many others, the character of these reactions strongly suggests an allergic mechanism. However, they do not fully satisfy the criteria of allergic reactions, for they rarely recur on subsequent administration. In fact, they possess the unique feature of usually disappearing while treatment continues. Until more precise understanding is reached, these skin responses must be regarded as allergic reactions of a peculiar sort. Incidence appears to be unrelated to dosage but can be correlated to some extent with duration of administration. They usually appear after two weeks of treatment, occasionally after only one but infrequently after four.

Four types of skin reactions may occur, either alone or in combination: (1) photosensitivity, (2) pruritus, (3) dermatitis, and (4) edema.

It has been demonstrated that chlorpromazine increases sensitivity of the skin to ultraviolet radiation.[11] In a small percentage of patients, possibly because of individual hypersensitivity, this may become clinically apparent in the form of predisposition to sunburn, hypersensitivity to heat, dermographia, and precipitation of skin eruptions and angioneurotic edema on exposure to sunlight. Pruritus, either localized or generalized, may be associated with photosensitization or may occur independently.

The figure of incidence of dermatitis varies widely from series to series, but is about 8 to 9 per cent. It is most frequent in the spring and summer, probably due to the photosensitization factor. Three forms can be recognized. The most common is an erythematous maculopapular rash, which often becomes vesicular or even bullous. Urticaria and erythema multiforme, occasionally hemorrhagic, are less common. Sites of predilection are the face,

neck, upper chest, upper extremities, or thighs, but there may be generalized spread. Antihistaminic drugs and topical antipruritic agents are of supportive value but provide only partial relief. Steroid hormones are almost never required. Even though the clinical appearance may be florid or even alarming, with rare exception the dermatitides resolve in from three to five days, whether or not treatment is stopped. If treatment is interrupted and later resumed, it rarely recurs. This is not true if dermatitis is due to contact allergy, which almost always recurs on repeated exposure. It also differs in clinical appearance, being of an eczematous type with edema, redness, vesicles, fissuration, and desquamation. Labhardt[24] reports the case of a nurse who had blepharoconjunctivitis and palpebral edema each time she came in contact with chlorpromazine.

Edema of the face, lips, and hands usually occurs in association with other skin manifestations and tends to be more persistent than the dermatitides.

*Hematologic Effects.* The changes in the blood picture that may occur during chlorpromazine therapy deserve special attention, for they indicate reactions that are the most likely to terminate fatally.

Several investigators[14, 18, 24] have found that following initial injections of chlorpromazine, the peripheral leukocyte count is decreased for several hours. During the course of therapy, leukocytosis, eosinophilia, leukopenia, and neutropenia may be observed. More often than not such variations are insignificant except to signal close observation of the hemogram. Leukopenia and neutropenia, however, may herald the most fearful of all chlorpromazine complications, agranulocytosis. A review of seven cases[7, 20, 26, 31, 33, 39] in the literature discloses a strong correlation among the factors of age, sex, and duration of administration but none with dosage. All were females; excluding 1 patient aged 38, all were at least 57 years old, the average being 64.9 years. In every case a minimum of 41 days had elapsed after onset of administration. Three cases were preceded by jaundice and/or rash. The mechanism of this complication is not defined, but the factor of sensitivity must be seriously considered. There are no consistent prodromal symptoms of agranulocytosis. Renewed lassitude and weakness occurring four to six weeks after onset of treatment indicates a complete blood count, for prompt detection followed by antibiotics, corticotropin, and transfusions may prevent death.

Other blood elements do not appear to be similarly affected by chlorpromazine. Rizzo and Russo[36] found that erythrocytes and hemoglobin decreased as did leukocytes after initial injections but that this was also transitory. Sedimentation rate is increased.[1] There have been rare cases of anemia, and "bleeding tendencies" have been described, but in general, disturbances of this type are confined to the late stages of agranulocytosis.

*Respiratory Effects.* Nasal congestion without rhinorrhea, and dryness of the oral and pharyngeal mucous membranes, are two of the most common side effects. Only rarely do patients volunteer these complaints, usually assigning them to acute coryza. These effects usually subside within the first few weeks but may persist when large doses are used. Dyspnea has been observed in association with prolonged tachycardia. We have observed an asthmatic attack in a patient without previous asthmatic history. An indirect effect on the respiratory tract is the development of pneumonia in elderly patients.[12] This may be

regarded as a preventable complication, in all probability the result of pulmonary hypostasis occurring during hypersomnolence.

*Musculoskeletal Effects.* Facilitation of the lower motor neuron by the reticular activating system (via the reticulospinal tract) is depressed by chlorpromazine. The result is subjective muscular weakness, a complaint second only to drowsiness in frequency. It is also one of the earliest, usually resolving within two weeks but renewable by increasing dosage. Constant at first, it may later be apparent only during periods of muscular exertion. In extreme cases there may be ataxia and incoordination. Related effects have been discussed above in relation to parkinsonism. Arthralgia, associated either with dermatologic reactions or as an independent finding, probably represents an allergic manifestation.

*Urinary Effects.* The disorders of urination that may occur are not believed to be primarily renal in origin. Moyer et al[30] found no evidence of acute renal toxicity or renal hemodynamic alterations either clinically or in laboratory experiments, although sodium and water excretion in animals increased slightly after parenteral administration. Patients receiving chlorpromazine drink excessive amounts of water because of mouth dryness, with resulting polyuria. Oliguria, which occurs much less frequently, is probably of neurogenic origin. Deep orange coloration of the urine that may be seen when dosage is high may be mistaken for bilirubinuria.

*Endocrinologic Effects.* Swelling of the breasts, frequently accompanied by secretion of fluid that has been found to be identical with mother's milk,[3] may occur in female patients receiving large doses of chlorpromazine. The swelling is diffuse and not associated with tenderness or cyst formation. In the author's series it occurred in women between ages 20 and 40 when doses were high. Increased sexual desire may occur, most commonly in females. In men the most common aberration is impotence. This discrepancy is not easily explained. Protracted amenorrhea is a rare complication. Bulimia and excessive weight gain have been described above in relation to the gastrointestinal system.

## PRECAUTIONS

Despite the multiplicity of side effects and complications, very few deaths have been reported. Certain precautions may minimize the occurrence of untoward reactions. When strict control is not possible, particularly when the patient is in the elderly age group, gradual increase of dosage may minimize changes in blood pressure and its associated symptoms. When signs of cerebral arteriosclerosis are present, intramuscular injections or initially high oral doses are unwise except when unusual indication exists. Since a significant number of patients who suffer complications have past histories of other allergic reactions, it should be prescribed in such cases with an awareness of the risks involved. It probably should not be given in cases of depression where retardation is prominent. Close observation of the blood picture is indicated if there is reduction of leukocyte count or if for no apparent reason the patient begins to complain of general malaise and weakness after these symptoms have originally cleared. The potentiation of barbiturates and narcotics by chlorpromazine appears to be overemphasized. There is no general agreement as to whether pre-existing liver pathology is a contraindication to chlorpromazine therapy; in the author's experience

it is not. Since chlorpromazine is being used so widely, it is becoming necessary to consider it in the differential diagnosis of every case of obstructive jaundice.

## COMMENT

As has been noted, the most characteristic feature of the side effects and complications of chlorpromazine therapy is their unpredictability. There are few drugs in which the factor of individual response is as significant. This high degree of unpredictability plus certain other features, however, may have important implications, offering perhaps a clue to the physicochemical process mediating the action of chlorpromazine.

Current theories attempt to explain the action of chlorpromazine as an inhibitory effect on the reticular formation, hypothalamus, and other structures with which they are intricately interrelated. On a descriptive level this hypothesis accounts for most of the side effects and many of the complications, but the explanation is only partially satisfactory. A constant pharmacodynamic action presumably affects the same structures in all patients so as to regularly produce a more or less uniform set of "side effects" at relatively similar dosage levels. Clinically this does not occur during chlorpromazine therapy. On the contrary, there is no uniformity in occurrence, type, or degree of untoward effects. The hypothesis also does not answer the question as to why most side effects can be expected to disappear even though administration is uninterrupted. It also does not explain, for example, why the occasional patient develops parkinsonism while receiving 800 mg./day while many others can tolerate many times that amount without any signs of basal ganglia involvement.

Certain parallels exist that seem to indicate that another factor must be present. It is well known that dermatitides due to chlorpromazine, which more than any others appear to be classical allergic reactions, disappear in the same way as the side effects, i.e., without the necessity of discontinuing therapy. Cases in the literature describe a similar course of events with jaundice and parkinsonism. There is much to support the belief that jaundice and agranulocytosis are expressions of allergic sensitivity. It should also be noted that many of the extrapyramidal syndromes due to chlorpromazine are of a postencephalitic character, and that toxic-confusional states can occur. Finally, just as acute allergic reactions may follow single doses of other drugs, dermatitis[9] and jaundice[38] have been produced by one dose of chlorpromazine. Parkinsonism has been produced within 24 hours after onset of administration.[2]

The question therefore arises of whether the side effects of chlorpromazine occur through the production of some unusual type of transient, self-limiting, allergic-like process of which the "complications" are merely the extreme manifestation. To support this theory it must also be postulated that sensitivity of this sort is extremely common in human beings and that the classical criteria of allergic reactions, which demand reproduction on subsequent administration, are not met. This hypothesis is far from unassailable but deserves further investigation.

## CONCLUSIONS

Chlorpromazine has many undesirable effects, most of which are transient and of rela-

tively minor clinical significance. Complications of potentially serious degree occur in a significant number of cases but generally resolve rapidly and without apparent residual effects. It appears that chlorpromazine is clinically a relatively safe drug, and that the therapeutic benefits which may accrue from its use outweigh the risks involved.

RESUMEN

La cloropromazina produce muchos efectos secundarios, la mayoría de los cuales son temporales y de importancia clínica relativamente escasa. Las complicaciones potencialmente graves tienen lugar en un número significativo de casos; pero, por lo general, se resuelven con rapidez y sin residuos aparentes. Parece que la cloropromazina es una droga relativamente segura desde el punto de vista clínico y que los beneficios terapéuticos que se pueden obtener con su uso, compensan los riesgos que envuelve.

RESUME

La chlorpromazine exerce plusieurs effets peu désirables, dont la plupart sont passagers et d'une importance clinique relativement minime. Des complications pouvant être sérieuses se presentent dans un nombre significatif de cas, mais en génèral elles se résoudent rapidement, sans résidu apparent. Il paraît que, du point de vue clinique, la chlorpromazine est un médicament sans changes, et que les bienfaits thérapeutiques obtenus par son emploi l'emportent sur les risques en question.

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# Some Considerations on the Use of Chlorpromazine in a Child Psychiatry Clinic

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The use of chlorpromazine in psychiatry has been largely restricted to adults. The major deterrent to the exhibition of this drug in the behavioral manifestations of children would seem to be the incidence of disturbing side effects. This appears to be an important argument against the usage of this drug when it has been traditional in the field of child psychiatry to rely only on psychotherapy and environmental manipulation. We have not observed disturbing side effects except drowsiness to date.

We have been interested in the combining of drug administration with psychotherapy in the child psychiatry clinic for more than four years. In May 1955 we reported our observations on the effect of the prolonged administration of chlorpromazine in 25 hyperkinetic emotionally disturbed children observed for periods up to 16 months.[1] This was, to our knowledge, the first controlled study reported with an extended period of observation. We have since extended our observations and in addition accumulated some unpublished data from other observers in the field of child psychiatry that should prove interesting.

Our observations in adults as well as the further reports of the diminution of attendant abnormal or excessive movements spurred us on[2, 3] to treat the hyperkinetic emotionally disturbed child. In our first 25 cases observed from 4 to 16 months, improvement in varying degrees was noted in 21 (84 per cent) and was marked in 70 per cent. Diminution in hyperactivity was the outstanding response, while assaultiveness was reduced considerably. The psychologic testing program as well as the clinical evaluation by the therapist and teachers suggested that the learning process was facilitated with definite improvement in the willingness to learn. Finally, trends toward increased emotional control were evidenced although the basic personality structure remained fundamentally unchanged. In the above group the team approach of establishing therapeutic relationships with both the child and the parents was not utilizable since 80 per cent of these children were either illegitimate or came from broken homes, and a parental figure was not available for cooperation. On the other hand, a smaller group of patients of similar background had responded satisfactorily to activity group therapy.[4] Because of a lack of therapists available for individual therapy, it was decided to extend the use of chlorpromazine therapy to the larger category of the primary behavior disorders of children as well as selected cases in every diagnostic group treated in our clinic.

There are now 30 boys and girls in the group of hyperkinetic emotionally disturbed children. In all categories 70 children are receiving the drug. The therapeutic indications

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varied from temper tantrums and frequent nightmares through disturbances in reading to the need for an immediate palliative procedure when psychotherapy was not initially available.

It is difficult to evaluate adequately the behavioral responses of children to any form of drug therapy because of the underlying influence of the associated interpersonal relationship. We discussed this aspect in the reported series where the children acted as their own controls, and 20 per cent showed a positive response to placebo medication. The remainder of the cases to be reported now did not.

We now, however, feel that we probably underestimated the psychic value of placebo therapy with children. A communication from Adamson[5] (Austin, Texas, Community Guidance Center) highlights this. In his double-blind study of 40 mentally defective children with severe behavior problems, 8 (80 per cent) of the first 10 children who were given the placebo showed improvement, a figure that dropped to 40 per cent when the first six weeks of observation were finished. Incidentally, 9 (90 per cent) of the 10 children receiving chlorpromazine showed improvement. Krush[6] noted the following sequence: 50 institutionalized children were given chlorpromazine and told it was "a means of helping you to get along better." During the first day, as the children were able to compare observations, they got the idea that these were actually vitamins to pep them up and a large number became much more active whether on placebo or on drug. On the second and third day word got around that they were getting a sleeping medicine, and a large number of the children spent much of these two days asleep or dozing, again unrelated to whether they received placebo or drug.

The general impression that relationship therapy in any form is effective with children would seem to be supported by these observations. The flexibility of the growing organism to adapt to various forms of treatment and changes in the environment both internal and external is certainly suggested. One can, therefore, appreciate the reliance of most child therapists on psychotherapy alone.

Nevertheless, there is a specific effect of chlorpromazine that can be observed in children. The report of Gatski[7] was followed by an exhibit at the American Medical Association convention in Atlantic City in June 1955, where Flaherty and Gatski[8] described the 45 children who were the most difficult conduct problems and who resisted "psychotherapy guidance and milieu therapy. When given various barbiturates they were still inaccessible to the therapist." After being treated with chlorpromazine for one week or longer, "39 of the 45 children improved . . . and continued to improve as they continued the drug. Having become amenable to supervision they were no longer resistant to psychotherapy . . ."

The above patients were hospitalized cases and for the most part not comparable to the other series reported thus far. Kinross-Wright[9] listed a series of 19 cases of behavior disorders in children who were ambulatory. Seventy-nine per cent responded favorably. He commented on the favorable responses seen in cases with brain damage that manifested hyperactivity and in 1 boy with multiple tics.

At this time we have observed the therapeutic response in 70 children ranging in age from 3 to 15 years. All of them have been outpatients. Our criterion for the use of chlorproma-

zine was not based on diagnostic categories. It was essentially the formulation that hostility or tension was underlying the complaints for which the parents brought the children to the clinic. Five of the children admitted to significantly disturbing fears, but as yet we have not been able to study the clear-cut effect in a child with a marked phobia.

The observation that was readily made by all observers was that hostility was diminished consistently in those children who had taken medication regularly for at least two weeks. Free-floating anxiety is not commonly complained of by children and therefore could not be studied adequately. However, it was noted by us that children did not routinely drop their fears of the dark, of ghosts, etc.

It was our impression that the primitive type of psychomotor response that Cannon labeled the fight-flight response was presumably influenced.[10] The treated children now seemed more willing to encounter and to tolerate new situations. The possible neurophysiologic basis for this has been described.[1]

Krush[6] has noted that a few schizophrenic children have become more regressed after medication. We do not doubt that a small number of children, particularly institutionalized cases, may show some evidences of withdrawal after treatment. We have not seen this degree of response in our cases. Two children we followed were described as worse in that they became more hostile. It was our feeling that we did not get adequate child-parent cooperation in these cases. So we would like to commit ourselves to the conservative observation that at least 3 out of 4 children were benefited to some degree while very few, if any, were made worse.

At this point one may ask, what are the contraindications? Thus far, we cannot list any that are clear-cut. The possibility exists that apathy and withdrawal may be accentuated, as Krush observed. We can speak only from the experiences with psychotic withdrawn adults, where we found the responses to be unpredictable and in many cases favorable. It is likely that further observation is necessary to determine contraindications as well as the most satisfactory technique for the termination of prolonged courses of medication in these children.

A comment that should be considered more than passing concerns our experience with 2 children with hitherto uncontrolled epilepsy who were controlled with chlorpromazine combined with anticonvulsives.[11]

The usual effective oral dosage in our series was found to be 25 mg. three times a day. The proper dose was determined clinically by the therapeutic response and the observation that the child's activities were not interrupted by drowsiness rather than by body weight. The maximum dosage was 300 mg./day. Flaherty[12] informed us that he used a wider range of dosage—60 mg. to 1000 mg. daily—in his series of institutionalized severely disturbed boys. The patient who was given 250 mg. four times a day developed some manifestations of parkinsonism that disappeared with dose reduction. Adamson[5] reports an average dosage of 300 mg./day with the range being 100 to 400 mg. Significant posologic modifications may evolve if combinations of chlorpromazine and reserpine or chlorpromazine and dexedrine now under trial prove more effective. The advantage of a single daily dose, especially for the school child, is obvious.

Do our experiences with children suggest new perspectives in psychiatry? We think so. There are the confirmed observations that overactivity in the spectrum ranging from restlessness through marked assaultiveness can readily be controlled. At the same time there is some evidence both from psychologic tests and from the reports of teachers and counselors that the child resumes the learning process. Such implications should encourage us in our work with both children and adults, for Freud[13] as well as Dollard and Miller[14] and others has stressed that psychotherapy must include re-education as well as resumption of the learning process.

Finally, we offer a speculation arising from the absence of a finding in children that is relatively common in adults. A number of observers have reported on the frequency of the complications of parkinsonism in chlorpromazine therapy in adults. The incidence ranges from 4.8 to 7 per cent[15, 16] in adults, while there is as yet no report on the incidence in children. This may simply be due to the fact that relatively few children have been treated in comparison with adults. But there is another consideration in the development of parkinsonism in children. The preliminary experiments were made by nature. We have known for the last 30 years that there is usually a difference in the postencephalitic sequelae of epidemic encephalitis in children, particularly between the ages of 3 and 10. They manifest destructiveness and impulsive behavior rather than parkinsonism.[17] Our observation and inquiries suggest thus far that chlorpromazine administration does not produce the complication of parkinsonism with the expected frequency noted in adults.[1, 5] This would take into account the reported relationship to the size of the dose. Should we assume that the child, in contrast to the adult, does not develop parkinsonism in response to noxious stimuli for biologic reasons, perhaps because the degree of adaptability of the young nervous system is different? We may find it easier to answer this when we have accumulated more data from the use of reserpine (which seems to be more "parkinsonogenic") as well as chlorpromazine in children.

Buerger and Mayer Gross[18] have theorized that ruminative thinking in postencephalitic parkinsonism was the response to the release of motor impulses that were turned into thoughts instead of being directly discharged. We have been impressed with the diminution in motor activity without the apparent development of ruminative thinking either clinically or in the test material in our subjects. Thus far in our studies of adults who developed parkinsonism we have not seen the expected increase in the incidence of obsessive thinking if the above theory were substantiated.

The idea has been put forth that the encephalitic process in children interferes with the development of superego manifestations in children.[19] Allowing for possible differences in brain areas influenced in epidemic encephalitis and those in the chlorpromazine effect, should we anticipate any distinctive superego effect in the long-term administration of the drug to the young child?

Do the child and the adult who develop a drug-induced parkinsonism have a psychic vulnerability exposed by the drug effect? Stengel[20] felt that such individuals were dealing with destructive impulses by freezing the movements through parkinsonism. We are pursuing further investigations, thus attempting to answer these questions. If some are

answered, perhaps chlorpromazine will have opened new perspectives in dynamic psychophysiology while fulfilling the hopes of pharmacodynamics.

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RESUMEN

Se presentan en este trabajo algunas observaciones basadas en la experiencia de los autores usando la cloropromazina en un amplio grupo de niños estudiados en la Child Psychiatry del Philadelphia General Hospital. Más de 50 niños hiperquinéticos, emocionalmente perturbados, han sido observados de 12 a 24 meses. Además, se ha estudiado la droga en otros estados, aunque la experiencia de los autores en los trastornos psicosomáticos ha sido particularmente limitada.

1. Se ha observado algún grado de mejoría en 3 ó 4 casos.

2. Los efectos de los placebos son significativos en los niños. Nuestros hallazgos del 20 por ciento son comparados con los de otros observadores.

3. Las complicaciones fueron mínimas. No se ha observado ningún caso de discrasia hemática. En muchos casos, se realizaron estudios hemáticos consecutivos. Tampoco se registró parkinsonismo ni dermatitis que necesitaran un tratamiento final.

4. Se aventura una teoría acerca del aumento de la flexibilidad de los mecanismos homoestáticos del niño en comparación con los del adulto. Ello es interesante no sólo en lo que se relaciona con la disminución de la incidencia de los efectos secundarios, sino también con la posibilidad de obtener una nueva perspectiva de la neurofisiología, que nos ayude a entender porqué los niños que desarrollan encefalitis epidémica tienen con más frecuencia "problemas de la conducta" que parkinsonismo.

RESUME

Des observations basées sur notre expérience avec la chlorpromazine dans un groupe important d'enfants étudiés dans le Child Psychiatry Clinic of the Philadelphia General Hospital sont presentées. Plus de 50 enfants hypercinétiques avec troubles emotionels etaient suivis entre 12 et 24 mois. En plus, la drogue a été employée sous d'autres maladies bien que notre expérience avec les troubles psychosomatiques soit très limitée.

1. Une certaine amélioration fut constaté dans 3 sur 4 cas.

2. Les effets avec l'emploi de placebos sont significatifs chez les enfants. Nos observations montrant un taux de 20% sont comparables à celles d'autres chercheurs.

3. Les complications furent minimes. Aucun cas de troubles sanguins ne fut observé, et dans plusieurs cas, des études en série furent faites sur le sang. On n'observa ni la maladie de Parkinson ni une dermite obligeant la cessation du traitement.

4. On avance une hypothèse sur la flexibilité supérieure des mécanismes homeostatiques

de l'enfant comparé a ceux de l'adulte. Celle ci est intéressante non seulement par rapport à la moindre incidence des effets sécondaires mais également par rapport à la possibilité d'ouvrir de nouveux aperçus dans la nevrophysiologie. Elle peut nous aider à comprendre pourquoi les enfants qui contractent l'encéphalite épidémique manifestent des problèmes de comportement plutôt que la maladie de Parkinson.

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# Psychologic Changes in Man after Chlorpromazine and Certain Types of Brain Surgery*

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## INTRODUCTION

Since its introduction in 1952, chlorpromazine has been increasingly used for a wide variety of psychiatric conditions and also for intractable pain. So highly is chlorpromazine esteemed that in a recent article in *The Lancet*, it was described as providing "a form of assistance unequalled by any other drug in our possession."[19]

Many of the conditions for which chlorpromazine is used are on occasion treated by brain operations. Indeed, this drug has been described and advertised as a "pharmacologic leukotomy." The comparison, moreover, between the influence of a leukotomy and of this drug on behavior has been made in almost every one of the articles dealing with its clinical aspects that have been published, although important differences in these effects are increasingly noted.

The extent to which these two forms of treatment are similar in their effects is a matter of considerable importance. There are obviously outstanding advantages in using a drug rather than a brain operation. Not the least among these is that as a better drug becomes available it can be utilized, often without any irreparable harm having been done, while an operation, once performed, is irreversible.

A leukotomy alters a man's temperament and even his character. We have attempted to find out to what extent chlorpromazine is similar to a leukotomy with regard to these effects on personality. What we have done is to contrast the personality changes as measured by a wide and varied group of objective tests before and after leukotomy, and before and after administration of this drug.

The results demonstrate that after these two forms of treatment, in one important aspect of personality, the personality changes are in opposite directions. The characteristic change after a leukotomy is a diminished score on all the personality tests characterizing an introverted population. Chlorpromazine has the reverse effect. Thus, while chlorpromazine and leukotomy both succeed in alleviating the condition of psychiatric patients, they seemingly achieve this by different processes.

## PATIENTS

Our report is based on a study of 24 patients treated with chlorpromazine, 58 patients subjected to three types of leukotomy, and 29 patients with operations in other areas of the

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orbital or cingulum region. The different groups of patients were comparable with regard to psychiatric condition and age.

## METHODS AND TESTS

Many of the personality tests we used were chosen to delineate the main dimensions of personality on which Eysenck[4, 5] and his associates in England have been working. It was found possible, by means of objective personality tests, to differentiate the anxious and depressed patients from the hysteric and psychopathic cases; and this group of measurements tended to cohere and to delineate a dimension. This dimension is referred to by us as "introversion." Similar investigations on neurotic and non-neurotic individuals yielded measurements delineating the dimension of "neuroticism." More recently measurements were identified that characterize a psychotic in comparison with a nonpsychotic individual. These personality tests were developed and adapted by us to measure those aspects of personality shown to have been changed by brain operations, and these have been described in detail in earlier publications.[6, 7, 16, 17] We used tests measuring five personality traits related to each of these dimensions. One group of tests differentiates between the introvert and the extrovert, the other group of tests between the neurotic and the non-neurotic. We also used personality tests related to five traits which appear to characterize the psychotic in comparison with the nonpsychotic individual. The Wechsler verbal and performance scale[20, 21] and the Porteus mazes[18] were used as measures of intelligence.

## CHLORPROMAZINE COMPARED WITH STANDARD LEUKOTOMY

First we will compare 19 patients (8 men and 11 women) treated with chlorpromazine in Paris and 20 patients (5 men and 15 women) subjected to a standard leukotomy carried out by McKissock in London. The mean age of the chlorpromazine patients was 42.9 years and of the leukotomy patients, 41.5 years. Chlorpromazine was administered orally and the dosage of 75 mg./day was kept constant for all patients. They were tested before the drug was administered and after it had been taken for an average of nine days. The interval between the two tests averaged three weeks. All patients subjected to a leukotomy were seen before the operation and after the traumatic effects of the lesion had subsided, an interval of at least six weeks. The pharmacologic and chemical properties of chlorpromazine are described by Courvoisier et al[1] and Dundee;[3] the standard leukotomy is described by McKissock.[10]

After these two forms of treatment, the changes on the personality tests tended to be in opposite directions. On the variables related to introversion, the chlorpromazine patient showed an increase, while the leukotomy patient showed a decrease. The chlorpromazine patient tended to decrease on the variables that characterize a psychotic individual. This is not so with a patient after a leukotomy (see table I). The chlorpromazine patient showed no loss on the intelligence tests used both in our investigations and in those of Lehmann and Hanrahan[9] in Canada. The standard leukotomy patient showed a significant loss on the

Wechsler verbal scale, on the comprehension subtest of this scale, and on the Porteus maze I. Q.

The most outstanding and statistically significant differences are in the personality traits characteristic of an introverted population. The contrast in individual personality traits related to introversion of the chlorpromazine patient and the leukotomy patient are shown in table II.

It should be noted that the psychopaths are at the extreme "extroverted" end of the continuum. The decreased introversion found after a leukotomy also means a movement toward the psychopathic end of the scale. Petrie reported in detail the accumulated ob-

TABLE I

*Changes after Chlorpromazine and Various Types of Brain Operations*

| | Treatment, number of patients, and classification | | | | |
|---|---|---|---|---|---|
| | Chlorpromazine 24 patients pain; mental | Cingulectomy 15 patients epileptic* | Standard leukotomy 24 patients neurotic† | Open rostral leukotomy 14 patients neurotic† | Selective surgery of areas 9; 10 19 patients pain; mental* |
| *Traits related to neuroticism* | | | | | |
| Speed of writing | Increased | Increased | Increased | Increased | Increased |
| Disposition rigidity | Decreased | Decreased | Decreased | Decreased | Decreased |
| Self-criticism | Decreased | Increased‡ | Decreased | Decreased | Decreased |
| Manual dexterity | Improved | Improved | Improved | Improved | Improved |
| Suggestibility | Decreased | Decreased | Decreased | Decreased | Decreased |
| *Traits related to introversion* | | | | | |
| Self-blame | Increased‡ | Increased‡ | Decreased | Decreased | Decreased |
| Accuracy (number of mistakes) | Increased‡ | Increased‡ | Decreased | Decreased | Decreased |
| Verbal I.Q./performance I.Q. | Increased‡ | No change‡ | Decreased | Decreased | Decreased |
| Orientation to present | Decreased‡ | No change‡ | Increased | Increased | Increased |
| Liking for sex humor | No change‡ | No change‡ | Increased | Increased | Increased |
| *Traits related to psychoticism* | | | | | |
| Fluency | Increased | Increased | Increased | Increased | Decreased† |
| Tempo of tapping | Increased | Increased | Increased | Decreased‡ | Increased |
| Concentration | Increased | Increased | Increased | Increased | Decreased† |
| Lowest score on track tracer | Worse‡ | Improved | Worse‡ | Worse† | Improved |
| Rate of passive fluctuation | Increased | Increased | Decreased‡ | Increased | Increased |

* Patients of Dr. Le Beau.
† Patients of Dr. McKissock.
‡ These are not changes in direction of decreased neuroticism, decreased introversion, and decreased psychoticism.

TABLE II

*Contrast of Individual Personality Traits Related to Introversion of the Chlorpromazine Patient and the Leukotomy Patient*

| Chlorpromazine | Leukotomy |
|---|---|
| Increased accuracy at manual and mental tasks | Decreased accuracy at manual and mental tasks |
| Undiminished verbal ability as compared to performance ability | Diminished verbal ability as compared to performance ability |
| Continues self-blame for unfortunate personality traits | Ceases self-blame for unfortunate personality traits |
| More orientated to the past than before | Lives primarily in the present |
| Likes sex humor somewhat less | Likes sex humor more |
| More endurance in a physical stress situation | Less endurance in a physical stress situation |
| Overrates his performance less | Overrates his performance more |
| Accepts responsibility for failure at a task | Considers failure at a task outside his area of responsibility |

jective evidence that an extensive leukotomy produces a less stringent conscience and causes a changed attitude toward the social environment.[16] It is important to draw attention to the fact that, in this area of personality, the results of chlorpromazine treatment differ from those of a leukotomy. Chlorpromazine does not cause changes that can be called antisocial, an effect which is in agreement with clinical observations.

It should be stressed that the change in the measures related to introversion is covered by a great quantity of research material. Decreasing introversion has been found consistently after the various types of leukotomy studied over many years.[6, 7, 12–17]

Clinical observation of the effects of chlorpromazine suggests "that excitory states are diminished and inhibitory states increased."[19] One of the complications reported after its use is a marked depression. Lieberman[8] reported an absence of unpleasant postleukotomy effects and good rapport and insight in chlorpromazine patients, in contrast to leukotomy patients. These observations, it will be noted, are also in agreement with the psychologic findings.

We also used tests differentiating the traits between psychotics and nonpsychotics, although for a relatively shorter time. The effects of chlorpromazine were in the direction of a decrease in "psychoticism" in all but one trait. (This one exception was not found when an additional 5 patients were examined.) However, the changes after the three types of leukotomy we studied were not consistently in the direction of a lessened psychoticism. There is some indication that psychotic scores increased after these operations, so that in this group of variables there is also a contrast between the effects of chlorpromazine and the effects of a leukotomy. It is of interest to note, in association with this finding, that chlorpromazine is reported to be particularly effective in managing the behavior of psychotic patients. Indeed, Lieberman[8] reported that several psychotic patients who failed to respond to a standard leukotomy improved considerably on chlorpromazine.

In fact, the only point at which there is any resemblance between the effect of the drug and the effect of a standard leukotomy is in the variables associated with "neuroticism." Both cause a decrease in neuroticism, but to a perceptibly different extent. After a leukot-

TABLE III

*Amount of Change after Chlorpromazine and Various Types of Brain Operations*

| | Chlorpromazine 19 pain & mental patients | | Cingulectomy 15 epileptic patients | | Standard leukotomy 20 neurotic patients | | Open rostral leukotomy 15 neurotic patients | | Selective surgery of areas 9 and 10 19 pain & mental patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean diff. | Stand. dev. of diff. | Mean diff. | Stand. dev. of diff. | Mean diff. | Stand. dev. of diff. | Mean diff. | Stand. dev. of diff. | Mean diff. | Stand. dev. of diff. |
| *Traits related to neuroticism* | | | | | | | | | | |
| Speed of writing | 0.35 | 12.03 | 4.79 | 22.75 | 7.55* | 13.56 | 13.43* | 10.75 | 5.63 | 14.76 |
| Disposition rigidity | −0.84* | 0.82 | −1.29 | 9.98 | −0.72* | 1.46 | −0.72* | 1.35 | −0.69* | 1.06 |
| Self-criticism | −0.27 | 3.09 | 0.38 | 5.45 | −6.84* | 10.12 | −5.00* | 6.16 | −0.82 | 6.15 |
| Manual dexterity | −5.61* | 10.54 | −9.00* | 13.00 | −6.75* | 7.43 | −9.77* | 13.35 | −6.77* | 8.79 |
| Suggestibility | −0.03 | 1.14 | −3.45* | 4.22 | −2.91* | 3.99 | −2.65* | 4.21 | −1.75 | 3.54 |
| *Traits related to introversion* | | | | | | | | | | |
| Self-blame | 0.61 | 2.87 | 1.00 | 4.24 | −7.84* | 9.97 | −2.33* | 3.89 | −1.65 | 5.59 |
| Accuracy (number of mistakes) | −2.67 | 24.47 | −14.36 | 46.97 | 5.55 | 18.25 | 4.92 | 27.38 | 2.46 | 14.23 |
| Wechsler verbal I.Q. | 4.21* | 8.18 | 8.19 | 9.15 | −7.51* | 10.31 | 2.02 | 6.75 | 0.71 | 11.78 |
| Wechsler performance I.Q. | 4.13* | 4.46 | 8.21 | 5.75 | 1.49 | 6.05 | 5.02 | 11.35 | 0.82 | 9.20 |
| Attitude to time | d.o.p. | | n.c. | | i.o.p. | | i.o.p.* | | i.o.p. | |
| Liking for sex humor | n.c. | | n.c. | | inc. | | inc.* | | inc. | |
| *Traits related to psychoticism* | | | | | | | | | | |
| Fluency (I) | 0.63 | 3.44 | 0.13 | 3.46 | 0.20 | 5.43 | 0.93 | 6.22 | −0.36 | 4.13 |
| Fluency (II) | 0.33 | 2.79 | 1.20 | 2.30 | 1.16 | 7.14 | 1.15 | 3.41 | −0.54 | 6.05 |
| Tempo of tapping | 5.61 | 15.01 | 9.18 | 39.04 | 1.11 | 18.62 | −17.75 | 13.56 | 9.88 | 29.50 |
| Concentration | 1.67 | 7.32 | 0.67 | 5.27 | 1.95 | 7.90 | 1.92* | 2.69 | −0.78 | 5.05 |
| Worst time score on track tracer | −7.61* | 17.29 | −25.95* | 39.74 | −15.00* | 11.48 | −17.63* | 21.82 | −16.21* | 13.88 |
| Worst error score on track tracer | 0.10 | 5.10 | −4.47 | 10.08 | 1.37 | 5.74 | 0.45 | 5.39 | 0.21 | 3.54 |
| Passive fluctuation | 4.00* | 5.28 | 1.17* | 1.80 | −1.12 | 7.84 | 1.92 | 8.31 | 1.00 | 3.69 |

* Significant differences.

† d.o.p. = decreased orientation to present; i.o.p. = increased orientation to present; n.c. = no change; inc. = increased.

omy, there is a more pronounced decrease. On three of the five variables, it is more than 10 times greater after the operation than after the drug (see table II). Thus, even in this area, there is a contrast between these two forms of treatment.

The self-portrait, consisting of a variety of personality traits, which the chlorpromazine patient draws is also different from that of a leukotomy patient. He shows awareness of his personality defects, whereas the leukotomy patient is self-opinionated, tending to gloss over his faults and to ascribe to himself desirable characteristics. It is of interest to note how the patient evaluates himself while he is under the influence of chlorpromazine. He describes himself as being less irritable, careless, uncontrolled, and ambitious, but more greedy; he is also less interested in the world around him.

One operation we studied that was very different in its effects from the various types of leukotomy was a cingulectomy. There is a striking similarity between the effects of chlorpromazine and of a cingulectomy on personality. The changes after a cingulectomy in 14 out of the 15 personality variables and in all the intellectual tests are in the same direction as after chlorpromazine (see table I). It should be pointed out, however, that while the pattern of changes of these two forms of treatment is almost identical, the extent of the change is greater after a cingulectomy than after the drug (see table III).

One of the major points of agreement in the many clinical papers on chlorpromazine is its quieting influence on aggressive behavior. Cingulectomy, which it most resembles, was first used by Le Beau in Paris because of its quieting effect on aggressive epileptics, and this has remained the most effective way in which this operation has been used there. The work, moreover, at the Lariboisiere Hospital indicates that the main function of chlorpromazine in clinical psychiatry is likely to be in quieting agitation, and that its effects on depressive states are unreliable and subject to individual variation. Physiologic research strongly suggests that the action of the drug can be explained primarily in terms of it being an antagonist of adrenalin.[2] The research, moreover, does not support the commonly held idea that the drug acts as a ganglion-blocking agent.

The similarity between the effect of chlorpromazine and the operation in the cingulum area may contribute to our understanding of the much discussed site of action in the central nervous system of this drug. Cingulectomy primarily involves Brodmann's areas 24 and 32. These differ from areas 9 and 10, the ones involved in the leukotomy type of operation, not only in their position but also because they are part of the agranular cortex and not of the granular cortex; their connections with the thalamus are with the anterior nucleus instead of the dorsomedial nucleus, and their connection with the hypothalamus is more intimate than is that of areas 9 and 10.[11]

The similarity between the effects of chlorpromazine and of a cingulectomy prompts another line of thought. Of the 24 patients examined under the drug, 9 showed some improvement, 7 showed only slight improvement, and 8 showed no improvement. Seven of the 8 patients showing no improvement were those with pain. Thus, although in the literature it is occasionally reported that the drug is useful in cases with pain, and a few of our pain patients do show some slight improvement, it does not seem to be consistently effective. Brain operations are also carried out for the relief of intractable pain. Cingulectomy, the

operation with which chlorpromazine has the most in common of the six types studied, is also ineffective in the relief of intractable pain in comparison with the leukotomy type of operation involving areas 9 and 10, even with the more limited techniques such as topectomy or cortical undercutting.

We suggested elsewhere that the aspect of personality that we have called introversion may be closely related to the intensity with which an individual experiences pain; and that the effectiveness of leukotomy in comparison with cingulectomy in helping patients with intractable pain may be due to decreased introversion.[6, 7, 16, 17] Chlorpromazine fails to show any indication of decreasing introversion and appears also to be relatively unsuccessful with patients suffering pain.

There is another aspect to the pronounced difference between the effect on personality of a leukotomy operation for pain and of chlorpromazine. We examined the differences between the patients most improved by chlorpromazine with those least improved; and between the patients most improved after leukotomy for intractable pain and those who were least improved. One of the characteristics of the successful chlorpromazine group is that they increase most in the introversion variables, while the successful leukotomy group decrease most. Thus, while we have been able to demonstrate the contrasted personality change in patients subjected to the two forms of treatment, irrespective of the degree of improvement, the contrast becomes even more pronounced if we compare the most improved patients of one group with those of the other. This further emphasizes the different ways in which these two forms of treatment achieve their end.

Moreover, prior to treatment, the successful chlorpromazine group had the lowest scores in the neuroticism variables, while the most successful leukotomy group had the highest scores. This finding suggests that there is a contrast between the kind of personality with which these two forms of treatment are likely to succeed.

It might be argued that, as the effects of chlorpromazine in contrast to cingulectomy are reversible, any "cure" which is achieved by its use must also be reversible; hence, no lasting improvement can be expected. It is, however, possible that "resting" a patient from his illness, even for a relatively short period, may have beneficial effects that are not reversible and that this is the manner in which chlorpromazine achieves its lasting results. The drug will achieve some but not all of the effects of a brain operation, and it is suitable only for certain types of cases. It can only be harmful in the long run by making extravagant claims for its achievements.

The dose of chlorpromazine, 25 mg. three times a day, was kept constant for all patients. We realize that this is comparable to the amount given to mild cases in other countries, and we propose to continue these investigations with patients to whom different doses are administered. The drug was given by mouth. It is reported to be rapidly absorbed from the intestine; the oral and intravenous doses required to produce symptoms of toxicity are about equal, with similar time intervals from administration to onset of symptoms.[19]

In studying the effects of chlorpromazine, we have been fortunate in having a large number of patients with well preserved personalities, many with intractable pain. This was also

the case with patients studied who were subjected to the brain operations. We feel that this has contributed to the clarity of the results.

In considering the meaningfulness of the differences in personality changes after the administration of chlorpromazine and after a leukotomy, it might be helpful to point out that the changes after a standard leukotomy were followed up first for a period of three months, then for nine months. The consistency of the results over this period permits considerable reliance to be placed on the pattern of personality changes. Moreover, the personality scores used were sufficiently sensitive to indicate differences in the degree of change resulting from less extensive operations.

In addition, a blind leukotomy was compared to an open one. In the former, the neurosurgeon has to rely on the external architecture of the skull; in the latter he has the additional help of the architecture of the brain. We have been able to show that while the pattern of personality change in the 10 variables is consistent, the variability of the change, as measured by the standard deviation, is greater after the blind operation than after the open one. It is interesting that the standard deviation of changes after the use of chlorpromazine is smaller than after any of the brain operations. Thus, while there is a great variation in the effects of this drug, this variation is smaller than that after the brain operations we studied.

SUMMARY

The pattern of personality changes, as shown by an extensive group of objective tests, found after the administration of chlorpromazine is pronouncedly different from that found after a leukotomy. The most outstanding differences are found on tests related to introversion. Chlorpromazine patients show increased scores on introversion variables, while leukotomy patients show a pronounced decrease.

Of the other types of operations studied which cause lesions in parts of the brain not affected by a leukotomy, we found that one, a cingulectomy, is strikingly similar to chlorpromazine in its pattern of personality changes. This finding is in agreement with clinical impressions of the effect of the drug and this operation.

Both the similarities and the differences between the effect of chlorpromazine and brain surgery appear to throw some light on why certain treatments are successful in relieving suffering with pain while others fail.

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**RESUMEN**

El cuadro típico de cambios en la personalidad, como se demuestra en un extenso grupo de pruebas objetivas, observado después de la administración de cloropromazina, es marcadamente diferente del hallado después de practicar la leucotomía. Las diferencias más sobresalientes se encuentran en las pruebas relacionadas con la introversión. Los pacientes tratados con cloropromazina muestran un aumento de puntos en las variantes de introversión, mientras que los tratados por leucotomía presentan un pronunciado decrecimiento.

En los otros tipos de operaciones estudiados y que causaron lesiones en partes del cerebro no afectadas por una leucotomía, se observó que una cingulectomía es sorprendentemente similar a la cloropromazina en el cuadro de cambios de la personalidad que origina. Estos hallazgos concuerdan con las impresiones clínicas sobre el efecto de la droga y sobre esta operación.

Tanto las semejanzas como las diferencias entre el efecto de la cloropromazina y la cirugía del cerebro parecen iluminar el porqué ciertos tratamientos tienen éxito en cuanto a aliviar el dolor mientras que otros fracasan en este respecto.

**RESUME**

Il se produit un changement considérable dans la personnalité des malades traités par la chlorpromazine et ceux qui subissent la leucotomie. La différence la plus importante se manifeste dans les tests ayant rapport à "l'introversion"; les malades traités par la chlorpromazine marquent des augmentations des variables dans le test, tandis que les malades opérés par leucotomie marquent une baisse importante.

Dans les autres types d'opérations étudiées par les auteurs, ayant affaire à des parties différentes du cerveau, la cinguléctomie produit des effets remarquablement semblables à ceux de la chlorpromazine. Cette donnée est d'accord avec les impressions cliniques sur l'effet du médicament et celui de l'opération. Les points de comparaison entre l'effet de la chlorpromazine et celui de la chirurgie du crâne jettent quelque lumière sur la raison pour laquelle certains traitements réussissent à soulager la souffrance avec algie, tandis que d'autres subissent un échec.

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## Psychiatry Meeting in Buenos Aires

The First Argentine Congress of Psychiatry, organized by the distinguished review, *Acta Neuropsiquiátrica Argentina,* will be held July 5 to 8, 1956, in Buenos Aires. The following program will be presented.

1. "The Teaching of Psychiatry and Training of the Psychiatrist." Moderators: Drs. Gregorio Berman (Córdoba) and J. A. Castedo (La Plata).

2. "Group Therapies and Human Relations." Moderators: Drs. Enrique J. Pichon Riviere and Jorge Mom (Buenos Aires).

3. "Psychiatric Demography and Social Welfare Institutions." Moderators: Drs. David Sevlever (Rosario), Raul Carrea (Buenos Aires) and Juan Soler (Córdoba).

4. "Psychiatric Manifestations in Vascular Disorders of the Brain." Moderators: Drs. T. Fracasi (Rosario) and Mauricio Costal (Tucumán).

5. "Early Diagnosis of Mental Illnesses." Moderators: Carlos R. Pereyra and Jorge Thenon (Buenos Aires).

6. Open Discussion.

# Clinical Research on Chlorpromazine and Reserpine in State and Private Psychiatric Hospitals

## A Comparative Review of the Clinical Problems

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The pages of medical history record the appearance of dramatic therapeutic agents or techniques that are initially hailed as the conquerors of disease and that quickly or slowly are finally allotted their correct position in the therapeutic armamentarium. In the history of psychiatry there is to be found a swinging of the pendulum so that at one period in time, hope is placed on the physical or organic approach and in another era, on the philosophic or psychologic approach. The past few years have seen the arousal of intense interest in pharmacologic agents, an interest that has produced some claims seemingly incredible in the light of present knowledge of the complexity of organization of the human psyche and the human body. A study of history enables one to forecast the relative place of these drugs in psychiatric treatment; already some, which within the past three years received widespread attention in the professional and public press, are no longer mentioned.

Until little more than a quarter of a century ago, the introduction of a new form of treatment would be received with the same enthusiasm as occurs today; the efficacy of the drug would be, in general, established by the private practitioner, who would find, by trial and error, the types of illness in which it was valuable, and also its limitations in those same forms of disease. With the emphasis on research today, a more "scientific" attitude is adopted: every patient becomes part of a study, every physician has his own criteria, and eventually a wealth of conflicting reports replaces the first enthusiastic papers; seldom is the final stage reached—viz., a number of well controlled independent studies by different workers using the same criteria, arriving at the real and accurate indications for the application of the technique. Somehow it is still the individual practitioner who plays the leading role in the final evaluation.

It is the purpose of this paper to demonstrate that the variation in the findings recorded by research workers in public and private hospitals represents part of this historical process and that such variations arise from emphasis on different aspects of the problem because of the particular needs, opportunities, and facilities characteristic of each setting.

Chlorpromazine and reserpine have for the past two years occupied the center of the research stage. Clinical investigations have been conducted by physiologists and biochemists, surgeons and anesthetists, internists and pediatricians, as well as by psychiatrists assisted by nurses, psychologists, occupational therapists, and social workers. Until the results are published, communication between workers, of necessity, is limited, and the interchange of knowledge and coordination of research activities is minimal, if not completely

absent. Already there has been the publication of thousands of studies, most of which cannot be compared with each other so that attempts at correlation of data are of little value.

The tremendous optimism about these drugs was aroused by consistently favorable reports appearing in the literature from various investigators in different parts of the country, and the first wave of enthusiasm led to their extensive use by most hospital physicians.[1–9] Almost all these reports emanated from workers in state hospitals who found that the behavior of disturbed, agitated, hyperactive, assaultive, and excited patients was greatly improved. The patients were more easily managed. They were quieter, less tense, and more amenable to suggestions from nursing and medical personnel. The need for physical and chemical restraints was reduced to a minimum. The incidence of accidents and of loss or destruction of personal and hospital property was significantly reduced. Also reduced was the need for electroconvulsive treatment, insulin coma therapy, and prefrontal lobotomy in certain patients. Some schizophrenic patients showed dramatic improvement in thinking, feeling, and behavior. They became quieter, less emotionally labile, less concerned about the content of their delusions and hallucinations, and less impulse-ridden in their behavior. Communications of thought and feelings to others improved to such an extent that some of the patients were more accessible to the conventional "interview" type of psychotherapy. Some patients improved so dramatically that they were able to leave the state institutions after years of confinement.

On the other hand, in the experience of investigators working in private practice or in private psychiatric hospitals, the usefulness of these drugs was found to be less spectacular.[10–13] They were effective in diminishing the intensity of behavioral and affective disturbances, but disorders of ideation, particularly in schizophrenic patients, responded scarcely at all.

In a controlled study conducted in our hospital, for example, over-all evaluation of the effects of chlorpromazine and reserpine was made in a group of 106 patients who received chlorpromazine and 103 patients who received reserpine. Improvement in affect and behavior was significantly greater than improvement in ideation. Although a significant number of these patients showed behavioral improvement, the degree of improvement was only slight to moderate. The psychiatric conditions for which these drugs were found to be most useful, in descending order, were: manic phase of manic-depressive psychosis; agitated and toxic states, particularly those associated with organic brain disease; schizophrenic reactions in which aggressive assaultive behavior is prominent; depressive reactions where agitation is present; and, least of all, neurotic reactions.

Among investigators in private hospitals there was agreement that emotional illnesses characterized by excitement were well controlled, but the best remission rate was obtained in disorders that are episodic in nature and that are known to be self-limiting in time. With the exception of depressive states, these are the same conditions that remit spontaneously or respond to electroshock. In psychoneurotic reactions, while anxiety appeared to be eased, the obsessions, phobias, and depressions appeared but little affected. More important in creating a less optimistic outlook was the small number of patients who responded in the manner described in the early reports.

It is obvious that a number of reasons must account for such difference of opinion. Comparison of patient populations points up important factors such as number, length of hospitalization, types of clinical picture, and differences in sociologic background.

In numbers alone, the public hospitals treat about 9 patients for every 1 in a private hospital. Most patients are referred to private institutions for intensive treatment and remain there for a relatively short duration. When quick remission is not obtained, they are frequently transferred to state hospitals. Relatively few families can afford long-term hospitalization in a private, intensive treatment center. This represents one form of selection, namely, that based on prognosis. A further selective factor probably exists in that a greater proportion of private hospital patients exhibit depressive features. The type of patient varies as regards clinical picture. Most private hospitals do not have facilities for the care and management of acutely disturbed persons whether they be excited and assaultive or deteriorated or withdrawn. Such patients are more likely to be found in state hospitals where a goodly proportion of the population is overtly disturbed, aggressive, agitated, dilapidated, and otherwise psychotic, requiring closed ward management. The therapeutic emphasis here is usually on behavioral improvement.

On the other hand, in the private hospital the level of social adjustment of the average patient is much higher and the purpose of the hospitalization is to obtain remission of the illness sufficient that the patient can return to the social level of the family. If the economic index is of any significance, this level is much higher than that of the individual patient in the state hospital. This demands that there be effected a return to "normal" in the ideational sphere as well as to a high standard of social adjustment including, especially for men, the capacity to return to remunerative employment consistent with the pre-existing income level. This brings to the fore the whole question of criteria of improvement, that much discussed and unresolved problem in psychiatric research.

The physician in the private hospital usually carries a low case load. Unhampered by administrative duties, he is able to establish psychotherapeutic relationships that enable him to have a close knowledge of the changes occurring in the patient. From a research viewpoint this has advantages and disadvantages. The advantages include a more precise evaluation of change; the disadvantages, the possibility that the improvement is due to factors other than the drug under study.

The state hospital in which research is an active interest of the staff is generally organized into a relatively small acute treatment center with a large portion of the population in custodial wards. The number of patients to each doctor in the continued care sections is usually in the hundreds, and more than a superficial impression of each patient is difficult to obtain. Yet the dramatic claims of the benefit of chlorpromazine and reserpine appear to refer to patients who have been on the long-term wards. Nothing could be more hopeful than the discharge of patients who have been hospitalized for a number of years. Most state hospitals are overcrowded as well as understaffed, with consequent pressure to provide accommodations for acutely disturbed persons. The net effect of this may be the establishment of a certain standard of improvement as the criterion to keep in balance the intake and discharge rates. Yet in some studies the discharge rate has been used as the indicator

of the efficacy of the new drug therapies. As Freyhan,[14] in common with others, has pointed out: "A high rate of discharged patients does not necessarily reflect the efficacy of any given treatment, since it may indicate nothing more than a liberal hospital administration. While conversely a lower discharge rate elsewhere does not exclude even better results with the same treatment, but represents a more conservative discharge policy of hospital authorities. Clinical improvement or administrative hospital status does not always coincide."

Not that with private patients there are no pressures for rapid discharge. In fact, these pressures may account for a large measure of the differences in attitude. Early reports indicated a wide fluctuation in dosages of the individual drugs with successive increments as the beneficial effects were not obtained. In private practice, the administration of drugs with possibly noxious side effects has to proceed in cautious fashion. For example, agranulocytosis with a number of chemical agents is well known, and the introduction of any new form of drug therapy must take this into account. The less important but sometimes unpleasant side effects may produce resistance on the part of the patient, and where the psychotherapeutic relationship is important, the ingestion of larger doses is not always easily obtained. With increasing knowledge regarding toxicity and its management—established usually in the state institutions—the private practitioner can more confidently urge the acceptance of the treatment by the patient. Thus the private hospital psychiatrist is in the respect of adequate dosage frequently behind his colleague.

The use of the newer drugs has brought out another significant difference. In private practice the establishment of sound interpersonal relationships is regarded as an essential criterion in arriving at improvement and recovery rates. Frequent visits by the family members, discussions with the doctor, the working out of problems of an interpersonal nature, all contribute to the adjustment of the patient on his return home. Many relatives have some knowledge of what is involved and what their role is in helping the patient readjust to community living. From personal communications it would appear that after many public hospital patients are discharged, the readmission rate is very high. Apparently the improvement, which is great in comparison with the previous level of hospital behavior, is still insufficient to allow reintegration into the normal family situation. The return of the person creates new problems for members of the family, each of whom has made his or her own adjustment to the absence of the sick one.

Whether a patient can be regarded as in remission will depend on the course following discharge. The private patients can afford to continue psychotherapy, supportive or uncovering, whereas there is a tremendous lack of opportunity for this for the patient who tends to enter a public institution. The experience of private hospitals has been that continuation of improvement obtained with the new drugs very often depends on the supportive efforts of the psychiatrist.

The occurrence of the spontaneous remissions in the various forms of mental illness still constitutes a major problem in the evaluation of psychiatric therapies. The general agreement on the usefulness of the new pharmacologic agents in the self-limiting episodic types of disorder raises the question: Is there a specific effect or do the drugs merely act as tranquilizers, tiding the patient over the acute stage? The conversion of manic episodes to

depressive states in short periods of time would seem to indicate a specific effect. That some long-term schizophrenic patients can be brought to the point of living outside a hospital is agreed, but most indications are that the outside environment must be a carefully prepared one. The principal findings are that long-disturbed patients can be generally controlled and improved only to the point that they can participate in a richer program of activity. The result of the new methods of treatment may well be that patients improve to the extent that better living arrangements and better physical programs with added cost will be necessary—without a significantly increased discharge rate.[15] Of great interest will be the readmission rates to both private and public hospitals of those discharged on chlorpromazine and reserpine.

There have been many drugs and techniques the use of which have appeared to produce significant results. It is now realized, however, that many of the beneficial effects have come from the increased attention given to the patient by the personnel whose own resignation to the chronic nature of their charges is lightened and indeed changed to optimism and enthusiasm by the prospect of a cure. On the other hand, the private practitioner, often having experienced disappointments in the past, tends to be conservative in his appraisal and frequently attributes any improvement to be due to his relationship with the patient rather than to the new medication. In the public hospital there is a better chance to evaluate the drug effect in purer form; that is, without the influences due to intensive interpersonal relationships.

Furthermore, with a large number of patients a better statistical appraisal is possible. This advantage in the state hospital is especially true during the introductory stages of the application of new drugs in ascertaining which illnesses are influenced both favorably and unfavorably. With a more representative mental hospital population, standard sampling is more accurate, the behavior of patients over long periods up to years is recorded, and there are available great numbers of patients who can remain under observation for long-term study. Contrast this with the private hospital, where research subjects may have to be discharged prematurely for financial considerations.

Thus the difficulties that confront the research psychiatrist are manifold regardless of the type of hospital setting in which he works. In a recent paper Hoch pointed out some of these.[16] Most important is the lack of a comprehensive methodology or a difference in methodology among research workers of various institutions. Criteria of improvement are judged by different psychiatrists in different ways because there is no agreement as to criteria. One psychiatrist may evaluate clinical improvement upon the patient's behavioral adjustment in the hospital. Another may base it upon the patient's social improvement or upon the amount of intellectual or affective insight he has gained, etc. "Some are satisfied if the patient returns to the premorbid level of adjustment. Others would expect a complete personality reconstruction before they call the patient recovered." Another difficulty is that many observations are made by investigators working independently. The isolated investigator is in danger of losing objectivity by virtue of the fact that he works alone. Often, such observations are testimonial in nature and rest on bias rather than on scientific, factual evidence. Furthermore, few studies have adequately controlled experimental design.

Even under ideal circumstances, it is difficult and time-consuming to design a scientifically controlled study. Evaluation of a new therapy is frequently made shortly after termination of treatment, and follow-up studies are either few or inadequate.

In spite of these deficiencies in the field of psychiatric research, progress is being made. It was most encouraging at some of the recent meetings of the American Medical Association and American Psychiatric Association and at symposia sponsored by pharmaceutical companies to provide a forum for the interchange of experience and observations among clinical research workers from different parts of the country. At one such symposium, only six months prior to the writing of this paper, the divergence of views between private and state hospital psychiatrists was well illustrated. From more recent reports, published and verbal, it is evident that the two groups are already much closer together. In the absence of the ideal research methodology, the over-all process by which the new drugs are being evaluated appears the same in principle as of old, but much accelerated; i.e., the potentialities or the general indications of the drugs are highlighted by psychiatrists in public hospitals, whereas refinements of application are made by the practitioner who works in a more intimate relationship with the individual patient.

RESUMEN

Los autores demuestran que la diversidad en los hallazgos obtenidos por los investigadores en hospitales públicos y privados, representa parte de un proceso histórico y que tal variedad surge de cómo se destacan diferentes aspectos del problema, las necesidades particulares, oportunidades y características de cada lugar. Ha habido comunicaciones altamente optimistas sobre la reserpina y la cloropromazina hechas por investigadores de hospitales del Estado que observaron mejoría en la conducta de los pacientes trastornados, agitados, hiperactivos, agresivos y excitados; la necesidad de represores físicos y químicos se redujo a un mínimo, como también la terapia por el coma insulínico, el electrochoque y la lobotomía prefrontal. Algunos esquizofrénicos experimentaron una mejoría espectacular en su manera de pensar, de sentir y en su conducta. Varios pacientes fueron más accesibles a la psicoterapia. En algunos casos, la mejoría permitió a pacientes hospitalizados por largos períodos de tiempo, salir de los hospitales del Estado. Sin embargo, en la práctica privada y en hospitales psiquiátricos privados, la utilidad de estas drogas ha sido menos espectacular. La intensidad de los trastornos de la conducta y de la afectividad se redujo, mas los desórdenes de ideación, especialmente en los pacientes esquizofrénicos, apenas respondieron. El mejor porcentaje de remisión se observó en los trastornos de naturaleza episódica y que se sabía eran de curso autolimitado. En las reacciones psiconeuróticas, la ansiedad pareció limitarse, pero parecieron ser sólo ligeramente afectadas las obsesiones, fobias y depresiones. El pequeño número de pacientes que respondió en la forma descrita en las primeras comunicaciones, creó una visión menos optimista.

Varios factores se consideran responsables de tales diferencias. Una mayor proporción de pacientes de los hospitales privados presentan estados depresivos; en los hospitales del Estado, una gran proporción presenta mayores probabilidades de sufrir trastornos más

intensos, son más agresivos, y más bien psicóticos, requiriendo ser tratados en salas cerradas. En estos casos, la importancia terapéutica reside en mejorar la conducta. En el hospital privado es más alto el nivel de reajuste social y el propósito de la hospitalización es permitir al paciente volver al ambiente social de la familia. Parece que el porcentaje de readmisiones de pacientes dados de alta en los hospitales públicos, es muy alto. La experiencia en los hospitales privados ha sido que la continuidad de la mejoría obtenida con las nuevas drogas, depende frecuentemente de los esfuerzos de ayuda del psiquiatra. Por otra parte, el hospital público proporciona una mejor oportunidad para evaluar el efecto de la droga en forma pura, sin las influencias debidas a la intensiva relación interpersonal. La población hospitalizada es más representativa, los datos que pueden obtenerse son más precisos. Existe un historial de la conducta de los pacientes por largos períodos y hay gran número de ellos que puede continuar bajo observación para ser estudiados sin tiempo limitado. En la práctica privada, la administración de drogas con posibles efectos nocivos tiene que hacerse con mucho cuidado. Los efectos secundarios de menor importancia, pero a veces desagradables, pueden producir resistencia por parte de los pacientes y, en donde la relación psicoterapéutica es importante, la ingestión de grandes dosis no siempre es fácil de obtener. Con el creciente conocimiento de la toxicidad y del empleo de los medicamentos, por lo general establecido en los hospitales del Estado, el médico privado puede urgir con mayor confianza la aceptación del tratamiento por parte del paciente. Con respecto a la dosis adecuada, por lo tanto, el psiquiatra del hospital privado sigue con frecuencia los pasos de sus colegas.

Existe una falta de comprensión metodológica entre los investigadores de varias instituciones. Asimismo, los investigadores que trabajan independientemente están en peligro de perder su objetividad, por trabajar solos. Hay pocos estudios con un plan experimental debidamente controlado. Sin embargo, se han hecho progresos: la potencialidad y las indicaciones generales de las drogas son destacadas por los psiquiatras de los hospitales públicos, mientras que su aplicación refinada es obra de los médicos prácticos que trabajan en una relación más íntima con el paciente individual.

**RESUME**

Les auteurs démontrent que la variation dans les observations notées par les chercheurs dans les hôpitaux publics et privés représente une partie d'un processus historique et que de telles variations proviennent de la mise en relief de différents aspects du problème par les besoins, les occasions et les facilités caractéristiques de chaque milieu. Divers chercheurs publient des rapports très optimistes sur la réserpine et la chlorpromazine dans les hôpitaux publics. Ils ont constaté une amélioration dans le comportement des malades troublés, agités, hyperactifs, aggressifs, et excités. Ils ont trouvé une réduction dans le besoin de contrainte physique et chimique, dans le besoin de thérapeutiques d'insuline, d'électro-convulsion et de la leucotomie préfrontale. Quelques malades schizophrènes montraient une amélioration frappante dans leurs modes de penser, d'agir et de conduite. Quelques malades devenaient plus accessibles à la psychothérapie par interview. Dans certains

cas l'amélioration permit aux malades hospitalisés depuis longtemps de quitter les hôpitaux publics. Cependant, l'utilité de ces drogues fut trouvée moins éclatante dans la pratique privée ou dans les hôpitaux psychiatriques privés. L'intensité des troubles affectifs et de comportement fut réduite, mais les désordres d'idéation, particulièrement dans les malades schizophrènes ne répondaient guère. Les meilleurs taux d'amélioration se produisirent dans les désordres de nature épisodique et connus comme étant limités dans le temps. Dans les réactions psychonévrotiques, l'anxiété parut soulagée, mais les obsessions, phobies et dépressions ne semblaient que legèrement affectées. Le petit nombre de malades qui répondaient de la façon décrite dans les premiers rapports donna une perspective moins optimiste.

Divers facteurs expliquent ces différences. Une plus grande proportion de malades dans les hôpitaux privés montrent des signes de dépression; dans les hôpitaux publics il est probable qu'une grande proportion montre des signes ouverts de trouble, d'agression et d'autres symptômes de psychose demandant une surveillance rigoureuse. Ici l'insistence dans la cure était placée sur l'amélioration dans la conduite. Dans l'hôpital privé le niveau d'adaptation sociale est plus élevé, et l'hospitalisation est faite dans le but de permettre au malade de retourner dans le milieu social de la famille. Il paraît que le taux de ré-admission des malades renvoyés des hôpitaux publics est très élevé. D'après l'expérience des hôpitaux privés la continuation de l'amélioration obtenue avec les nouvelles drogues dépend souvent des efforts supplémentaires du psychiatre. D'autre part, l'hôpital-public offre une meilleur occasion d'évaluer l'effet de la drogue en sa forme pure, sans les influences qui résultent des relations interpersonnelles intenses. La population des malades est plus représentative, l'echantillonage-standard plus exact. Le comportement des malades est noté pendant de longues périodes, et un grand nombre de malades peuvent rester sous observation pour une étude de long terme. Dans la pratique privée l'administration de drogues dont les effets peuvent être nocifs doit se faire avec prudence. Des effets secondaires, moins importants mais parfois déplaisants, peuvent produire, de la part du malade, quelque résistance, et quand la relation psychothérapeutique est importante, l'ingestion des doses plus grandes n'est pas toujours obtenue avec aise. Avec la connaissance croissante de la toxicité, établie habituellement par les institutions publics, le médecin privé peut suggerér ce traitement à ses malades avec plus de confiance. En ce qui concerne le dosage efficace, donc, le psychiatre de l'hôpital privé est souvent en retard sur ses collègues.

Il manque aux chercheurs de diverses institutions une méthodologie comprehensive. Aussi, les chercheurs, travaillant indépendamment, risquent-ils de perdre leur objectivité parce qu'ils travaillent seuls. Il y a peu d'études ayant un projet expérimental sufisament controlé. Cependant, on fait du progrès; les psychiatres dans les hôpitaux publics soulignent les potentialités ou les indications générales des drogues, alors que le médecin privé, travaillant dans une relation plus intime avec le malade, fait les raffinements d'application.

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## International Symposium on the Diencephalon

An International Symposium dealing with the relationship between the diencephalon and endocrine glands, organized by the Milan Section of the Italian Society of Experimental Biology, will be held May 3, 4, and 5 in the Sala delle Colonne of the Museo della Scienza e della Tecnica, Piazza S. Vittore 21, Milan.

The program will consist of presentations on the diencephalic control of endocrine activity, followed by open discussion on each topic.

For additional information write to Segretariato Symposium sul Diencefalo, Dr. S. B. Curri and Dr. L. Martini, c/o Istituto Farmacologia Università de Milano, Via Andrea del Sarto 21, Milan.

## Clinical Psychopathologic Conference

# Fatal Hyperpyrexia during Chlorpromazine Therapy

*Frank J. Ayd, Jr., M.D.*

BALTIMORE, MD.

It is now well established that chlorpromazine in the usual therapeutic doses is a relatively nontoxic compound. It can cause many bothersome side effects that are seldom serious and that subside with continued administration of the drug or may be controlled by the addition of other drugs to the patient's medication. However, this compound is not without its potentially serious side reactions and may even prove fatal. The purpose of this report is to record a fatal reaction to chlorpromazine and to caution against the indiscriminate use of this drug.

### CASE REPORT

A 41 year old white man was hospitalized for chlorpromazine therapy for a schizophrenic reaction, unclassified. His past psychiatric history revealed the presence of overt schizophrenic symptomatology for four years. He had been treated with several courses of electroconvulsive therapy that produced a temporary amelioration of his symptoms. Several months prior to admission this patient had been treated with doses of chlorpromazine up to 400 mg./day with some symptomatic improvement. When chlorpromazine was discontinued the patient relapsed.

On admission, physical and neurologic examinations were negative. The psychiatric examination revealed an agitated schizophrenic with paranoid features. This patient was placed on increasing doses of chlorpromazine to a maximum of 2500 mg. on the eighteenth treatment day. On the nineteenth and twentieth treatment days he received 2500 mg. daily. On the twenty-first tre .tment day he had had 1800 mg. At 6:00 p.m. his temperature was normal. Two hours later he suddenly collapsed. His rectal temperature was 108 F. He had a few epileptiform seizures and lapsed into a coma. Intensive treatment of the hyperthermia lowered the temperature to 104 F., but he expired nine hours after his collapse.

### NEUROPATHOLOGIC FINDINGS

Unfortunately only the brain of this patient could be obtained for post-mortem study.* A summary of the gross and microscopic findings suggests an intense process causing profound swelling of neuron cells associated with increasing capillary distention and terminal petechial hemorrhages. The lesions seen would be compatible with intense thermoregulatory disturbance such as would be seen with heatstroke. Anatomic lesions of a destructive nature were not present. The only reliable lesions seen were acute swelling of neurons, particularly

* Neuropathologist: Dr. John A. Wagner, Dept. of Pathology, Division of Neuropathology, University of Maryland, School of Medicine, Baltimore.

in the thalamus and hypothalamus, and intense congestive changes and petechial hemorrhages, which were present throughout the entire brain.

## DISCUSSION

Fluctuations of temperature in patients receiving chlorpromazine have been reported. This drug, at any dose level, may cause mild hyperthermia (99 to 101 F.) or hypothermia (96 to 98 F.) in the initial stages of therapy, which subsides as treatment is continued. In a few patients, daily elevations or drops in temperature have been recorded throughout the treatment period. This has occurred most often in patients receiving large doses (500 mg. or more daily).

Chlorpromazine may cause sudden elevations of temperature (up to 105 F.) accompanied by profuse perspiration and some feelings of prostration. This febrile reaction, which subsides after a few hours, is not related to the dosage of chlorpromazine, the route of administration, the climatic environment, or the physical activity of the patient. It may occur once or repeatedly in the first two weeks of treatment, after which time it is rare.

Chlorpromazine also may cause striking hypothermia in the early stages of treatment. The temperature may be as low as 93 F. During this period the patient is lethargic, and the usual defense mechanisms to conserve body heat such as piloerection and vasoconstriction are impaired. Within a few hours the temperature returns to normal. Further treatment with chlorpromazine does not cause a recurrence of hypothermia.

These clinical observations indicate the chlorpromazine may affect the function of the hypothalamus, which is the main center for the regulation of body temperature. In cats and monkeys, injury to the rostral part of the hypothalamus causes hyperthermia, while injury to the region dorsolateral to the mammillary bodies results in hypothermia. The hyperthermia and hypothermia produced by chlorpromazine are transient, indicating that this drug in therapeutic doses causes a temporary biochemical impairment of the function of the neurons of the hypothalamus.

The influence of chlorpromazine on the temperature-regulating mechanism may be affected adversely by the environmental temperature. In cold weather many patients taking 300 mg. or more daily report hypersensitivity to freezing temperatures. In hot, humid weather many patients mention a hypersensitivity to the temperature. Some complain that the heat is almost intolerable whenever the temperature rises above 90 F. A few perspire excessively and manifest symptoms of mild heat prostration. This increased sensitivity to heat is not related to the dosage of chlorpromazine, although patients on large doses apparently are more sensitive.

In the case under discussion the fatal hyperpyrexia occurred at a time when the environmental temperature was high. Goldman[1] reports that 8 of his chlorpromazine-treated patients had nonfatal heatstrokes during the torrid temperatures of the summer of 1955. These clinical observations suggest that environmental temperature may enhance the action of chlorpromazine on the thermoregulatory mechanism. This is supported by the experimental studies of Berti and Cima,[2] who found that the toxicity of this drug is accentuated by environmental temperatures. Finally, Ranson[3] and his collaborators in experiments

on cats and monkeys found that destructive lesions in the preoptic and supraoptic regions between the anterior commissure and the optic chiasma are followed by hyperthermia when the animal is exposed to a degree of heat that would have little effect on the body temperature of a normal animal.

Although no anatomic lesions in the brain were found that could account for the death of this patient, it is postulated that his demise was due to the toxic action of chlorpromazine on the hypothalamus and that the toxicity of chlorpromazine was accentuated by the environmental temperature.


RESUMEN

La cloropromazina, a cualquier dosis, puede causar fluctuaciones en la temperatura corporal. Este compuesto parece sensibilizar a los pacientes a las temperaturas ambientes extremas, como lo demuestra el caso de una hiperpirexia fatal durante la terapia con cloropromazina. El paciente, un esquizofrénico crónico, estaba recibiendo grandes dosis de cloropromazina durante una ola de calor. Alrededor del vigesimoprimer día de tratamiento sufrió una súbita hiperpirexia (temperatura de 42,2° C.) y falleció a las nueve horas.

Se le hizo una autopsia parcial. Los estudios neuropatológicos del cerebro revelaron un intenso proceso que produjo un gran edema de las neuronas acompañado de distensión capilar y hemorragia petequial terminal. Se observó edema agudo de las neuronas, particularmente en el tálamo y el hipotálamo.

Se discute en este trabajo la influencia de la cloropromazina en el mecanismo regulador de la temperatura. Se presenta la evidencia fisiológica para ilustrar la influencia de las lesiones destructivas en el hipotálamo sobre la regulación de la temperatura.

Aunque no se hallaron lesiones anatómicas en el cerebro, éstas deben considerarse como causantes de la muerte de este paciente que se produjo por la acción tóxica de la cloropromazina sobre el hipotálamo. La toxicidad de la cloropromazina fue acentuada por la temperatura ambiente.



RESUME

La chlorpromazine, à n'importe quel dose peut causer des fluctuations dans la température du corps. Ce composé semble rendre le malade plus sensible aux etrêmes de la température ambiante ainsi qu'il fut demontré dans un cas d'hyperpyrexie fatale pendant la cure par la chlorpromazine. Le malade, un schizophrène chronique, recevait de fortes doses de chlorpromazine pendant un temps de grande chaleur. Le vingt et unième jour du traitement le malade souffrit une soudaine hyperpyrexie (temperature 42° C.), et mourut dans les neuf heures.

A l'autopsie, des études névropathologiques suggèraient un processus causant un grand enflement des cellules neurones, associé à une distension capillaire et des hémorraghies pétéchiales. Un sévère enflement des neurones etait observé, particulièrement dans le thalamus et l'hypothalamus.

L'influence de la chlorpromazine sur le mecanisme régulateur de la température est

discutée. L'évidence physiologique est presentée pour illustrer l'influence sur la température de lésions destructrices de l'hypothalamus.

Bien que nulle lésion anatomique sur le cerveau ne fut trouvé pour expliquer la mort de ce malade, il est supposé que sa demise fut causée par l'action toxique de la chlorpromazine sur l'hypothalamus et que la toxicité de ce medicament fut accentuée par la température ambiante.

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## MD Publications' Technical Display at AMA Meeting

MD Publications, Inc., will be represented again this year at the 105th Annual Meeting of the American Medical Association, which will be held in Chicago from June 11 to 15. The 1956 display booth of MD Publications will feature (1) Antibiotic Medicine & Clinical Therapy, the current developments in this dynamic field of medicine; (2) Stress, the revolutionary concept in medicine; and (3) Travel Medicine, a new branch of medicine dedicated to health in travel.

Prominently displayed by MD Publications will be their seven journals: Antibiotics & Chemotherapy; Antibiotic Medicine & Clinical Therapy; International Record of Medicine; Quarterly Review of Pediatrics; Journal of Clinical and Experimental Psychopathology & Quarterly Review of Psychiatry and Neurology; Quarterly Review of Surgery, Obstetrics and Gynecology; and MD.

Books published by MD Publications, Inc., and Medical Encyclopedia, Inc., during the past year will also be exhibited. These include: Fifth Annual Report on Stress 1955–56 by Hans Selye and Gunnar Heuser; The Impact of the Food and Drug Administration on Our Society (by 67 authors); Antibiotics Annual 1955–1956 (150 papers by 375 authors); Symposium on Medicated Feeds by 57 contributors; The MD International Symposia Monographs—(1) Health and Travel, (2) Medical Writing, (3) Psychiatry and Religion. Books in the Antibiotics Monograph Series are Erythromycin by Wallace E. Herrell; Assay Methods of Antibiotics by Donald C. Grove and William A. Randall; Tetracycline by Harry F. Dowling; Antibiotics in Nutrition by Thomas H. Jukes; Polymyxin, Neomycin, and Bacitracin by Ernest Jawetz.

# Dr. Albert H. Holland, Jr., Appointed Clinical Consulting Editor of Antibiotic Medicine & Clinical Therapy

The Editors of ANTIBIOTIC MEDICINE & CLINICAL THERAPY, Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D., are honored to announce that starting with the June issue Albert H. Holland, Jr., M.D., Medical Director of the Food and Drug Administration, will join their editorial board as Consulting Editor. In this role Dr. Holland will be primarily responsible for scientific selection and editing of all material relating to clinical therapy.

Dr. Holland was on the editorial board of the *Journal of Southern Research*.

ALBERT H. HOLLAND, JR.

Prior to his appointment as Medical Director of the Food and Drug Administration on March 31, 1954, Dr. Holland was Medical Director of The Armour Laboratories in Chicago. Before joining Armour in July, 1950, he was Director of the Office of Research and Medicine at the Oak Ridge (Tenn.) Operations of the Atomic Energy Commission. He also served as Medical Adviser to the Manhattan Engineering District project at Oak Ridge, having been assigned originally by the Army as Medical Liaison Officer. Dr. Holland's service at Oak Ridge covered a period of approximately four years, from 1946 to 1950. Dr. Holland received his medical degree from the New York University College of Medicine in 1944, interned in the New York Post-Graduate Hospital, held an Assistant Residency at Memorial Hospital for Cancer and Allied Diseases, and was Resident in Internal Medicine at the Post-Graduate Hospital. He is the author of a great many scientific papers and is a distinguished medical lecturer.

The Editors are also pleased to announce that with the June issue the scope of AM&CT will be enlarged to include, in addition to the present material on the clinical use of antibiotics, original papers, abstracts, news, and advanced reports on the clinical use of all chemotherapeutic agents, such as the sulfonamides, vitamins, hormones, tranquilizers, and others. The Editorial Board will be enlarged to include distinguished figures in all branches of American and international medicine. ANTIBIOTIC MEDICINE & CLINICAL THERAPY is published by MD Publications, Inc.

# QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

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INCORPORATING INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY

# FOREWORD

The purpose of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY is to present promptly brief abstracts, noncritical in character, of the more significant articles in the periodical medical literature of Europe and the Americas.

For readier reference, the abstracts are classified under the following general headings:

PSYCHIATRY

1. Administrative Psychiatry and Legal Aspects of Psychiatry
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13. Syphilis of the Nervous System
14. Treatment
15. Book Reviews
16. Notes and Announcements

In fields which are developing as rapidly as are psychiatry and neurology, it is obviously impossible to abstract *all* the articles published—nor would that be desirable, since some of them are of very limited interest or ephemeral in character. The Editorial Board endeavors to select those which appear to make a substantial contribution to psychiatric and neurologic knowledge and which promise to be of some general interest to the readers of the REVIEW. Some articles, highly specialized in character, or concerning a subject already dealt with in an abstract, may be referred to by title only at the end of the respective sections.

A section entitled INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

The Psychiatry and Neurology Newsletter was compiled by Doctors Leon Epstein and Francis N. Waldrop.

The Editorial Board at all times welcomes the suggestions and criticisms of the readers of the REVIEW.

WINFRED OVERHOLSER, M.D.
*Editor-in-Chief*

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

# Has Chlorpromazine Inaugurated a New Era in Mental Hospitals?

*Winfred Overholser, M.D., Sc.D., L.H.D.*

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The use of drugs in the treatment of mental patients is nothing new. In ancient Greece black hellebore was considered such a specific drug that advice to take a trip to Anticyra, where the shrub grew plentifully, became a common expression. The soothing effects of opium have long been known, and this drug was frequently prescribed even 100 years ago. Later such sedatives as paraldehyde, chloral, and the barbiturates were developed. These various drugs have had their respective vogues, depending upon the prevailing knowledge of pharmacology and on the rationale of their administration. In more recent years, however, there has been considerable reluctance to use sedative drugs because they were looked upon as merely substitutes for mechanical restraint, as something not therapeutic but merely palliative. Furthermore, such drugs as paraldehyde and the barbiturates, if they quieted the disturbed patient, did so at the expense of impairing his consciousness and even of bringing about stupor. Most of the sedatives used hitherto have likewise been at least potentially toxic or addictive, or both. There have been other periods when drugs were but little used, or when other supposed "cures" dominated the scene, only to lose their popularity. In recent years the vogue of psychotherapy has, at least in the minds of some, obscured the fact that certain physical approaches can aid in treating mental disorders.

Thanks to the ingenuity of French science, something entirely new in the line of sedatives has appeared on the horizon, namely, chlorpromazine. This drug exhibits the unusual quality of bringing about sedation and quiet without substantial impairment of consciousness. It has a wide range of tolerability, is largely nontoxic, and is not addictive. Serious side-effects have been rare, and the effects which have occurred have been almost entirely reversible. Thus, although chlorpromazine is far from being a panacea, it is nevertheless a most useful drug that has demonstrated its wide usefulness wherever used. It has been

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Address presented at International Colloquium on Chlorpromazine and the Neuroleptic Drugs in Psychiatric Practice, Paris, France, October 20–22, 1955.

found useful in several fields of medicine, as in the control of hiccough, nausea and vomiting, the reduction of postanesthetic shock, and obstetrics. It is primarily, however, in the practice of psychiatry and especially of hospital psychiatry that I would speak. An example of the widespread use of the drug in the United States is found in the fact that probably as many as four million patients have had it prescribed for them!

The medical literature is full of the reports of the use of chlorpromazine, and it is obviously impossible to summarize these reports here. Much is yet to be learned about the pharmacologic action of the drug, about the criteria for its prescription, and about the elimination of side-effects. Differences of opinion have been expressed as to the optimum dosage, as to the duration of the administration of the drug, whether or not maintenance doses should be continued for an indefinite period. A full evaluation must necessarily wait for a longer period of observation of the effects. There is no doubt, however, that many new vistas have been opened and that changes have been noted, particularly in hospital psychiatry.

Let us consider first the effects on the patient himself. The opinion seems to be almost unanimous that patients who exhibit psychomotor activity, assaultiveness, hostility, and negativism show a reduction in their motor output with the administration of the drug. They are less restless, are quite ready to sit quietly, are less assaultive and destructive, are orderly and well-behaved. Subjectively they exhibit a marked reduction in anxiety. They are clear mentally, in good contact with their surroundings, and are able to discuss their hallucinations and delusions calmly and with a considerable degree of objectivity. Thus, many patients who had previously been inaccessible now become amenable to psychotherapy and the other forms of occupation and recreation which are provided for them on the wards. Although in certain cases of agitated depression a certain amount of quieting has been noted, the drug is not recommended for the depressions in general, particularly those without agitation, electroshock still being practically specific here. Shock therapy in general, which has been used in some hospitals for the treatment of catatonic symptoms and overactivity, has been reduced to a vast degree. At Saint Elizabeths Hospital, for example, in comparable six-month periods of 1954 and 1955 it was found that the number of patients was reduced from 177 to 13 and the number of treatments from 1168 to 107. Restraints in general have been used much less, and at Saint Elizabeths Hospital we have found that the need of seclusions of our disturbed patients has been greatly reduced. Approximately 10 per cent of our patients are receiving tranquilizing drugs, over half of them receiving chlorpromazine and the others receiving reserpine, a combination of the two, or some of the other tranquilizing drugs.

One controlled study of 50 Negro women at Saint Elizabeths Hospital was reported recently by Drs. S. Tenenblatt and A. Spagno. They found 80 per cent of the patients improved. Here it should be borne in mind that as in many of the other reports it was the patients who were the most disturbed and had the least good prognoses who were given the drug. The best results were noted in the treatment of the manic-depressive and the schizophrenic psychoses, particularly the catatonic and paranoid types of the latter. Of 50 patients under treatment only 4 required discontinuance of the therapy on account of untoward effects. Many of the patients who responded had been ill for years and were serious ward problems.

There is no question whatever concerning the tranquilizing effect of the drug on disturbed patients, particularly in those suffering from the paranoid type of schizophrenia and the manic phase of manic-depressive psychosis.

What of the effect on the ward as a whole? Briefly, the atmosphere of disturbed wards has been completely revolutionized. Patients now remain clothed; they are quiet; they do not annoy each other; they conform to the conventions, take an interest in their personal appearance and in the appearance of the ward. Since the patients are more receptive and more cooperative they demand other activities to occupy them during their waking hours. There is thus a far greater need for the development of recreational, occupational, and diversional therapies, of more psychotherapeutic attention to the patients, of greater interest on the part of the nurses and attendants in providing various programs. Far from reducing the number of problems the drug has merely changed them; there are indeed more problems now than there were before, but these all operate to the advantage of the patient.

What of the effect on the staff and the personnel? A far greater interest has developed. The morale has been increased. A hopeful attitude has come about as patients who had been previously troublesome were noted to be cooperative and helpful and to show other signs of improvement. The psychiatrist has been returned to medicine, as has the nurse, not only by the administration of the medication, but by the increased necessity of attention to possible signs of adverse effects. It has been a challenge to the entire medical and ward personnel to increase attention to the patient and to show more interest in bringing about his improvement, while to the psychiatrist there has been offered an opportunity for a better study of psychopathology, since the patient is now able and willing to discuss his problems, whereas before he might have been entirely inaccessible to investigation and help.

What is the effect on the hospital as a whole? We have already mentioned the decrease in the destructiveness and assaultiveness, the wear and tear on the physical plant and on the clothing. What of the statistics? This is something which must wait for a later evaluation. In some hospitals, as in ours for example, the initial study was done on the most disturbed, least hopeful patients. Although greater freedom has been permitted them as a result, this has not been reflected as yet in a substantial increase in the discharge rates. Many patients are, however, out on temporary visit, and if their improvement holds it is quite likely that they will be discharged from visit in the fairly near future. It has been observed in some hospitals, notably at the Rochester (New York) State Hospital, as reported by B. Pollock, that the number of patients returned to the hospital from trial visit has decreased greatly. There is thus a hope that the number of discharges may be increased and that patients may continue at home with or without maintenance doses of the drug, while at the same time it is not at all impossible that the number of first admissions will be reduced by the use of the tranquilizing drugs in the community. Sound statistics are not available at the moment as to the duration of hospitalization. As a matter of fact, too, the rate of discharge is subject to a number of misinterpretations and is not necessarily a sound criterion of therapeutic success. It seems quite likely that more activity in out-patient departments and community clinics will be called for as a result of the drug.

What of the effects of the drug on the family of the patient? There has been a marked

increase in the hopefulness of the families and in their expectation that their loved ones may be returned to them soon. Unfortunately, in the case of some of the patients who have been in the hospital for a considerable period of time and who have been psychologically "given up" by the families, there appears to be now on the part of some of these families a fear that the patient may be released! Sometimes, indeed, this fear borders almost on panic. These cases are, of course, exceptional. In general it certainly must be said that the attitude of the family has been vastly improved.

Finally, what of the effect on the community? These drugs have again made the mental hospital a medical institution in the minds of the public. Physicians in general practice are more cooperative and more willing to refer patients for hospital or other psychiatric treatment. Some physicians in the community who are not psychiatrists are using chlorpromazine to treat mild cases of mental illnesses. Legislative bodies have shown a greater interest in the problems of mental illness, now that a positive and easily administered therapy appears to be available, and the interest of various community groups, such as churches, and other civic groups has been greatly stimulated. Families have not only become more hopeful but more demanding. Very often indeed they are insistent that the drug be administered, whether or not it be medically indicated! Also, the community is at last developing an attitude of far greater tolerance toward the discharged mental patient, a greater readiness to accept him back into the community and into industry or his former occupation.

Mention has been made earlier of the fact that there are some complications which are observed from time to time in treatment with chlorpromazine. We have noted, for example, at Saint Elizabeths Hospital in one group of Negro women that 36 per cent of the group exhibited the presence of colostrum or milk in the breasts. This is a symptom which has not been frequently noted in the literature; it is, like most of the other symptoms, entirely reversible and quite insignificant. A fairly common complication, especially if the use of the drug is continued over a period, is a parkinsonian tremor, often decidedly marked. The tremor, however, subsides promptly when the drug is discontinued. The incidence of jaundice appears to be in general moderate only, and in almost all cases apparently completely reversible when the drug is discontinued. The same may be said of the fever, the photosensitivity of the skin and the erythemas which have been sometimes observed. More serious is the incidence of decrease in white cells, sometimes going to a stage of clinical agranulocytosis. Several cases of death from this cause have been reported. In hospital practice it seems clear that the drug should not be prescribed without occasional tests of liver function and blood counts. If fever occurs, this may be a warning signal and calls for special vigilance. Hypotension has been reported, and emotional depression has been noted in certain cases. It should be remembered that *no* drug that has any beneficial effects whatever is without some potential dangers. Most of the side-effects of chlorpromazine are reversible and the only one which causes a threat to life (fortunately relatively rare) is agranulocytosis, as already mentioned.

Any discussion of chlorpromazine should not fail to mention another drug of an entirely different source that has closely related effects, namely, reserpine. It is the impression of some of the workers in the field that reserpine acts somewhat better in organic cases such

as the arteriosclerotic group than does chlorpromazine. It is perhaps somewhat less effective in women than in men. It is slower in action and more cumulative in effect. The mental effects of the drug are related, although the action is less dramatic; it has been noted by some observers that there appears to be a synergism between this drug and chlorpromazine, so that combined therapy may be useful. As with the use of chlorpromazine, a reversible parkinsonism is frequent. The dangers of hypotension are even greater with reserpine than with chlorpromazine, and the presence of gastric ulcer is a decided contraindication. A few deaths have been reported from acute edema of the glottis. The incidence of unfavorable side-effects is somewhat less than with chlorpromazine.

Some of the "Philistines" may object that both of these drugs, that is, chlorpromazine and reserpine, are merely palliative. This is no criticism of a drug, even though it be meant as such. There are many drugs which are valuable although not basically curative. One has only to think of insulin in diabetes, of liver extract in pernicious anemia, of vitamin therapy in certain of the avitaminoses, and so on. It may be said that after all the anesthetics are merely palliative, since they do not cure pain. There is a place for palliatives in the practice of medicine! Most emphatically we have in chlorpromazine and reserpine two drugs which add greatly to the comfort, first of the patient, of his family, and of those about him. Furthermore, by allaying anxiety and reducing motor activity while at the same time maintaining clarity of consciousness, the patient becomes far better able to make human contacts, to accept psychotherapy and to profit by it. As long ago as 1914 Freud (who after all began his professional life as a pharmacologist) suggested that "all our provisional ideas in psychology will some day be based on an organic substructure." He went on to say: "This makes it possible that special substances and special chemical processes control the operation of sexuality and provide for the continuation of the individual life in the species."

Today much valuable work is being done by pharmacologists in cooperation with psychiatrists. One thinks of the experimental use of mescaline, of lysergic acid, of serotonin, as well as of the "tranquilizing" or "neuroleptic" drugs. More knowledge is needed about their action. Much more work needs to be done in the development of other pharmacologic agents, which may be as effective without having the undesirable side-effects.

In the light of our knowledge regarding the psychic effect of the new drugs, is it too fantastic to suggest that perhaps some day those psychoses which we now term, for want of a better word, "functional," may be found to be due in part at least to endogenous chemical substances which act on the central nervous system, and even perhaps if that fact should be established, that chemical antagonists may be developed as therapeutic agents?

There have been many swings of the pendulum in psychiatric treatment—the "moral treatment" of Pinel, the bloodletting of Rush, the "focal infection" era, the prolonged sleep and insulin period, the various psychotherapeutic approaches. Now the pendulum seems to have swung again, this time into a pharmacologic era. This era will bring psychiatry closer to the rest of medicine, and will make our patients more amenable to psychotherapy, both individual and group, and to the other adjunctive therapies. It will increase our knowledge of mental functioning, and most important of all, will aid our patients in their restitution to health and to society.

# What Causes Alcoholism

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Why does one person become an alcoholic while another who drinks just as much or more does not? Why is it that once a person loses control over his drinking he can never again drink moderately? Why does an alcoholic continue to drink even when he knows that he might lose his health, his wife, his job, or the respect of his friends? These and other questions as to what causes a person to become addicted to alcohol are often asked by, and of, the physician.

Many attempts have been made to explain alcoholism on the basis of a single cause. For example, Strecker[1] has said that alcoholism is due to immaturity. Others have implicated latent homosexuality or a domineering father or an overindulgent mother. Williams[2] believes that alcoholism is due to vitamin and mineral deficiencies. Smith[3] has attributed alcoholism to a deficiency in the pituitary-adrenal-gonadal triad.

That such a complicated disease as alcoholism could be due to a single cause would seem highly improbable. On the contrary, it is evident that each alcoholic drinks for his own special reasons. These can be grouped for discussion under the following general headings: social, habit, psychologic, constitutional, and physical.

## SOCIAL FACTORS

Most people start to drink because it is the socially acceptable thing to do. The pressure to continue drinking, whether it agrees with one or not, is terrific in our modern American culture. Drinking is fostered not only by social custom but also by advertising, movies, and television, which picture the man of distinction with a drink in one hand and a bottle near by. The person who does not drink socially may be rejected as being odd or priggish.

The alcoholic therefore often feels and is made to feel lonely, isolated, and resentful because he cannot drink like other people. In his desire to rejoin the ranks of the social drinker, he makes repeated disastrous efforts to drink moderately even when experience has taught him that this is no longer possible. In about 1 drinker out of 20, moderate social drinking gradually changes into a vicious habit leading to uncontrolled pathologic drinking.

## HABIT

The habit-forming properties of alcohol have not been sufficiently stressed in the medical literature. Alcohol should be grouped with the barbiturates and narcotics as a drug (for it is a drug) that can produce physical as well as psychologic habituation.

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Read before the Section on Nervous and Mental Diseases at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 8, 1955.

Alcohol is not normally metabolized by the brain cells. However, with prolonged drinking, the metabolic pattern is apparently changed so that the presence of alcohol is a temporary necessity for optimum brain functioning.[4] The brain cells become so dependent on the presence of alcohol that its sudden withdrawal throws them, for the time being, into disequilibrium, which is translated into the symptoms of hang-over, tension, tremors, delirium, or even convulsions.[5] The patient is often tempted to continue drinking in the hope that he can ward off these distressing withdrawal symptoms. Apparently, there can be a cellular as well as a psychologic craving for alcohol.

Fleetwood and Diethelm[6] have carried out some interesting investigations concerning another biochemical effect of alcohol. They have found that alcohol neutralizes certain adrenergic, cholinergic, and other unknown substances in the blood that are associated with the emotions of anxiety and resentment. Apparently, alcohol relieves some of the physical as well as the psychologic concomitants of tension.

From the psychologic standpoint, it is well known that drinking can become such a deeply ingrained habit that it becomes a devastating way of life. Once a person is caught in the web of the drinking habit, its grip can be broken only by total and permanent abstinence. A few alcoholics will be able to stop by themselves,[7] but most patients either will continue to drink or will be able to quit only with outside spiritual or medical help. Why one person becomes enslaved by the drinking habit while another does not depends on the individual's susceptibility to alcohol, his stability, and the degree of psychologic pressure that is driving him to drink.

## PSYCHOLOGIC FACTORS

Much has been written about the psychologic causes of drinking. Most of this can be summarized by saying that alcoholism is an escape (albeit a temporary and futile one) from all the trials and tribulations of life. Alcohol gives a false feeling of courage to the fearful, confidence to the insecure, absolution to the guilty, and superiority to the inadequate. It gives solace to the lonely, sleep to the insomniac, rest to the weary, relaxation to the tense, calmness to the disturbed, and oblivion to the desperate. As a suicidal equivalent, alcoholism may even be an escape from life itself.

Alcohol offers temporary escape not only from worries and troubles but also from boredom. There are many alcoholics who have no real problems except that they have exhausted all of life's adventure that can be obtained with money or success. Because of a depletion of inner resources, they no longer know what to do with themselves except to drink.

Although these psychologic causes of alcoholism are extremely important and have received a great deal of attention in medical literature, they are by no means specific to this disease. All of the psychologic factors that are said to have caused alcoholism can be found in nonalcoholic individuals.

Fortunately for mankind, as Kant[8] has pointed out, the avenue of escape through alcohol is open only to certain people. Most persons, including many who are suffering from severe neuroses, find drinking to be no escape but only more trouble.

Why some people can escape from their conflicts and frustrations through alcohol, while others who are just as emotionally disturbed or more so cannot, is not fully understood. The answer, however, goes deeper than simply the desire to escape. We have all known patients who have deliberately tried to drown their sorrows in alcohol but have been unable to do so because drinking only made them feel worse.

Just as there is no specific psychopathology of alcoholism, there is no characteristic personality pattern that is typical for the alcoholic. The only trait that all alcoholics have in common is their intolerance to alcohol. Apparently, the alcoholic is so constituted that alcohol reacts differently on him than on the normal drinker.

## CONSTITUTIONAL FACTORS

One difference between the alcoholic and the normal drinker seems to be a constitutional peculiarity of the alcoholic's pharmacologic reaction to alcohol. The alcoholic gets a special glow and release from tension that is not enjoyed by the average drinker.

Another bit of evidence for a constitutional predisposition to alcoholism is seen in those patients who have trouble with alcohol from the very beginning of their drinking history. Although these cases are in the minority, when they do occur, there is usually a family history of alcoholism that suggests a hereditary predisposition.[9] It is interesting, in this connection, that a strain of mice can be bred that voluntarily consume more alcohol than the ordinary run of mice.[10]

It is in this area that the greatest advances are likely to occur in the prevention of this disease. If those who are predisposed could be detected early and educated regarding their innate susceptibility to alcoholism, the incidence of problem drinking might be materially reduced.

Most alcoholics, however, give a history of years of normal controlled drinking before they gradually and insidiously slip over into uncontrolled pathologic drinking. This loss of control over drinking might be called the specific factor (the factor X) in the etiology of alcoholism. It is the one common denominator that is characteristic of all alcoholics. All treatment, including psychoanalysis,[11] is predicated upon the fact that once control is lost over drinking, it can never be regained, no matter how effective therapy may be in straightening out the associated personality disorder. This loss of control is due partly to psychologic and constitutional factors, but mostly it is due to physical changes that take place in the brain after years of heavy drinking.

## PHYSICAL FACTORS

Consideration of the physical basis of alcoholism has been much neglected, especially as it contains the key to the reason why the alcoholic, once he has developed this disease, can never again drink moderately. Those few cases in which control is regained are so rare that they should be diagnosed as pseudoalcoholics rather than true alcoholics.

It is well known that alcohol can permanently damage the brain. Courville and Myers[12]

have given an excellent description of the gross and microscopic cortical atrophy that takes place in the frontal and parietal surfaces of the brain in chronic alcoholism. In addition to the irreversible damage produced by alcohol itself, there may be an associated encephalopathy caused by vitamin B deficiency, which so often accompanies chronic alcoholism. Tumarkin et al[13] have demonstrated by psychologic tests, pneumoencephalography, and electroencephalography that this brain damage can and does occur even in young alcoholics who have indulged in repeated bouts of heavy drinking.

It is safe to say that in many people, heavy drinking causes a gradual dropping out of brain cells. It is also logical to assume that the first cells to be affected would be those that are first anesthetized by alcohol, namely, those subserving the higher cerebral levels of will power and judgment. The brain reserve is gradually and insidiously whittled away until the stage is reached where any alcohol in the system will immediately paralyze the patient's will power and judgment. Few alcoholics intend to drink to excess, but once alcohol is imbibed, they are left helpless to control their drinking. That part of their brain that tells them when to quit becomes anesthetized. This is why it is impossible for the alcoholic to drink moderately and why once control is lost, it is never regained. Brain cells once lost are never replaced.

The damaging effect of alcoholism on other organs such as the liver, the adrenal cortex, and the kidneys, as well as avitaminosis, often adds to the general morbidity of this disease. The resulting physical exhaustion leads to the vicious circle of "pick-up drinks" in an effort to keep going.

## SUMMARY AND CONCLUSIONS

1. Alcoholism is caused by a number of different factors, among which are the following: (a) the pressure of social custom; (b) the force of habit; (c) the psychologic escape potentialities of alcohol; (d) a pharmacologic idiosyncrasy that causes the effects of alcohol to be more attractive and less obnoxious to the alcoholic than to the average drinker; (e) a constitutional predisposition that causes some people to lose control over alcohol early in their drinking history; (f) brain damage from long-continued drinking that causes some people gradually to lose control over alcohol; (g) general physical depletion from excessive drinking leading to the vicious circle of "pick-up drinks" to keep going.

2. The one common denominator (the factor X) of alcoholism is the inability to drink moderately. This is caused by a constitutional or acquired intolerance to alcohol. When alcohol enters the system, there is an immediate paralysis of will power and judgment that leaves the patient helpless to control his drinking.

3. Once control over alcohol is lost, this is permanent, because tolerance once lost is never regained, or brain cells replaced. The only way that the alcoholic can control alcohol is through total and permanent abstinence.

4. The alcoholic's compulsion to drink, even when he knows that he should not, is based on the force of habit, the effort to drink socially again, and the urge to escape painful psychic tensions.

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# ABSTRACTS

# psychiatry

## ALCOHOLISM AND DRUG ADDICTION

35. *Alcoholism as a Medical Problem.* G. LOLLI, New Haven, Conn. Bull. New York Acad. Med. *31*:876–885, December, 1955.

The personality of the addictive drinker is discussed from the angle of the physiologic, psychologic, and social factors that contribute to its physiognomy. Alcoholism is defined as a search for a blended pleasure of body and mind, appealing to some individuals only—the alcoholics. The links between alcoholism, an extreme deviation of the drinking habit, and obesity, an extreme deviation of the eating habit, are discussed.

The basic mechanisms underlying a shift from uncontrolled drinking to total and permanent abstinence require the liberation of emotional energies so that the latter can be used to keep the addictive urge to drink in check.

At present only psychosocial approaches, either professional or lay, have chances of success.

Tentative areas for research in the field of physiology, psychology, and sociology are outlined, together with the basic goals of prevention and education. Prevention and education are considered of paramount importance—insofar as they reach beyond alcoholism into the general field of mental health.—*Author's abstract.*

36. *Current Attitudes to Alcoholism of Psychiatrists in Southern California.* MAX HAYMAN, Beverly Hills, Calif. Am. J. Psychiat. *112*:485–493, January, 1956.

The one approach most favored for alcoholism by psychiatrists in Southern California who answered a questionnaire is membership in Alcoholics Anonymous. Ninety-nine per cent of them approved Alcoholics Anonymous, and 80 per cent had referred patients to the organization. Yet they believed only 10 per cent of the persons who join A.A. remain sober for over two years. This, against the claim of A.A. that 60 per cent or more of their fellowship are recovered, emphasized the pessimism of the psychiatrists questioned.

Ninety per cent of the psychiatrists who replied said they do not treat alcoholics or that they limit the number or the type they will accept for treatment. They obtain recovery, they said, of 10 per cent of patients, improvement of 50 per cent, and the rest are unchanged.

The emphasis in psychiatry is on elimination of the anxieties leading to alcoholism; in Alcoholics Anonymous the emphasis is on the strength to bear these anxieties. Ninety per cent of the replies received were in favor of clinics for alcoholics, and the respondents felt that governmental agencies should support these clinics. Under such circumstances psychiatrists would combine their abilities with psychologists, social workers, and Alcoholics

Anonymous. Thirty-five per cent of psychiatrists said they are willing to work in a clinic, the majority without recompense. 7 references. 2 tables.

37. *The Sexual Adjustment of Alcoholics.* JACOB LEVINE, West Haven, Conn. Quart. J. Stud. on Alcohol *16*:675–680, December, 1955.

A study was made of the clinical records of 79 alcoholics (63 men and 16 women). All information pertinent to their sexual adjustment, which was obtained in the course of psychotherapeutic interviews, was reviewed and analyzed. The data showed that these alcoholics nearly all had sexual problems of one sort or another. In most instances these patients showed a diminished interest in heterosexual relations. In many instances this diminished sexuality appeared to be of long-standing duration and could not be attributed to the excessive use of alcohol alone. It was also found that a large proportion of the male alcoholics came from homes with an overpowering and controlling mother, upon whom they were greatly dependent, and a passive and distant father, toward whom they felt hostile. —*Author's abstract.*

*For Reference*

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## BIOCHEMICAL, ENDOCRINOLOGIC, AND METABOLIC ASPECTS

39. *The Capillary System in Patients with Psychiatric Disorders.* JOHN W. LOVETT DOUST, Toronto, Canada. A. M. A. Arch. Neurol. & Psychiat. *74*:137–143, August, 1955.

An interest in the relevance of tissue anoxia to psychiatric disorders led to a study of the capillary systems of these patients. Heralding this study, an investigation is reported of resting capillary blood pressures in 67 healthy persons and in 100 patients representative of seven psychiatric diagnostic groups. The technique employed was an indirect one, stemming from the work of Lewis' associates 40 years ago and using a Hooker capsule applied to the dorsum of the hand. Correlation of the results obtained from the control group with those of Eugene Landis using his direct nailfold capillary microintubation technique showed the Hooker method figures to correspond with those of the direct method when cannulation was made at the tips of the capillary loops.

It was found that the mean capillary pressures of all the psychiatric patient groups were significantly higher than that of the controls. The highest means occurred in the organic dements and schizophrenics, while those of the depressive patients, psychopaths, and neurotics showed the least differences from the control values. Age (between 18 and 62 years) did not contribute significantly to these results.

No correlation was found between capillary and simultaneous systolic arterial blood

pressures, but a significant relationship was established between a rising capillary pressure, a rising capillary hemoglobin level, an increase in capillary fragility (diminishing capillary resistance), and a falling capillary blood-oxygen saturation. 36 references. 2 tables.—*Author's abstract.*

40. *Influence of Chlorpromazine and Alcohol on Cerebral Hemodynamics and Metabolism.* JOSEPH F. FAZEKAS, S. N. ALBERT, AND RALPH W. ALMAN, Washington, D. C. Am. J. M. Sc. *230*:128–132, August, 1955.

The effects of the administration of chlorpromazine and alcohol, alone and in combination, on cerebral hemodynamics and oxygen utilization were studied. Despite blood levels from 100 to 200 mg. per cent, alcohol exerted no significant effect on the rate of cerebral blood flow or oxygen utilization. Chlorpromazine administered intravenously in concentrations up to 300 mg. per cent was also without effect on these functions. When both were administered simultaneously in concentrations of approximately the same magnitude, the findings for cerebral blood flow and metabolism were not appreciably altered from normal values. The degree of central nervous system depression achieved by the combination of drugs was not great, and the patients could be readily aroused. Those patients who were clinically disturbed by the ingestion of alcohol were tranquilized by chlorpromazine. The potentiating effect of chlorpromazine on alcohol administration is discussed. 11 references. 3 tables.—*Author's abstract.*

## CLINICAL PSYCHIATRY

41. *Brainwashing as a Factor in Psychiatric Illness.* PETER S. SANTUCCI AND GEORGE WINOKUR, Baltimore, Md. and St. Louis, Mo. A. M. A. Arch. Neurol. & Psychiat. *74*:11–16, July, 1955.

More important than the social and political implications of brainwashing is its role in producing human behavior of a grossly aberrant or defensive type. It can produce forced behavior as seen in the cases of those who deserted the United States Armed Forces, but more important is its function in the possible production of psychiatric syndromes in the thousands of returned men from Korean prisoner of war camps. This paper reconstructs the method of brainwashing and presents some of its varied results by the use of interviews with former prisoners. It reviews the case of a returned prisoner of war who had been brainwashed and who, upon his return to the United States, suffered a mental illness. There are also elaborated testable hypotheses. The two hypotheses are: (1) the choice of not being repatriated, a choice several men took, was behavior that could be considered defensive because it protected these men against conflict, and (2) because of the intensity of this conflict, there will be more mental illnesses among the men returned from Korea than in a comparable group from the general population or from the German or Japanese prisoner of war camps of World War II, keeping the time since release constant in all three groups.

Indoctrination was usually subtle, with attempts to destroy group identification and to

establish self criticism and isolation. By making the prisoner of war grateful to an enemy who said he would not be harmed, by repetitiously offering instruction in controversial social and political subjects, and by minor rewards of praise, food, or better conditions for their cooperation, a strong conflict pattern was established. This simple method of establishing confused and erratic behavior by producing a conflict when distinction cannot be made between external stimuli that are closely related in type, but that have widely divergent results, was done in Pavlov's laboratory by showing a circle to an animal and feeding it, and showing it an ellipse and not feeding it. Gradually the circles were made flatter until the figures were hardly distinguishable from each other, and the animal did not know whether to anticipate food or not. This same experiment applies in the methodology of brainwashing in that the prisoner is rewarded for "having an open mind" on controversial political and social subjects and is not rewarded for being "reactionary." If the preliminary concept of a circle is clear, there is little difficulty in distinguishing it from an ellipse, but if the preliminary concept of what makes a circle is indefinite or incomplete, there is greater danger of future confusion and erratic behavior. An analogy to this can be seen if one considers the prisoners' backgrounds, their attitudes toward the captors, and their subsequent difficulty in separating what they believed as loyal Americans and what was infiltrated into them by indoctrination. Those men whose social and political philosophies were firm and determined before becoming prisoners were less subject to conflict under pressure and less responsive to it. 6 references.—*Author's abstract.*

42. *Somato-Psychotherapeutic Approach to Long-Term Schizophrenic Patients.* IAN C. FUNK, LEO SHATIN, EARL FREED, AND LEONARD ROCKMORE, Albany, N. Y. J. Nerv. & Ment. Dis. *121*:423–437, May, 1955.

This was the first report of a comprehensive psychiatric treatment program designed to improve the ward adjustment of long-term schizophrenic patients. It described results obtained during the first 15 weeks of study. A variety of treatment modalities was utilized, including electroshock therapy and with special emphasis on group psychotherapy. The program was undertaken to demonstrate the potentialities for improvement of long-term schizophrenic patients.

Experimental (demonstration) and control patients, 10 in each group, were individually matched for age, chronicity, and ward adjustment. Mean age was 56.2 years for the demonstration group and 58.6 for the control. Mean chronicity (years since first hospitalization) was 26.7 years for the demonstration group and 26.9 years for the control. Ward adjustment for the two groups was closely comparable, as quantified by a behavioral rating scale developed for the specific purpose. Educational level and socioeconomic status were equivalent. Control subjects proceeded with their usual ward treatment programs, but all demonstration subjects were combined into a social unit and transferred into a separate and open ward. Two group psychotherapy sessions were conducted daily. Other treatments included corrective therapy, hydrotherapy, music therapy, occupational therapy, pharmacologic therapy, recreation, and EST. The personnel of this demonstration ward, together with the rehabilitation staff, participated in special group meetings and discussions. All patients were studied at the beginning of the experiment and at stated intervals thereafter. Techniques

employed were: Behavioral Rating Scale, Multidimensional Scale for Rating Psychiatric Patients, Weekly Rating Scale, and brief psychomotor efficiency tests. The ensuing data were quantified.

At the fifteenth week (cut-off date of this report), the demonstration patients had attained statistically significant improvement over the control patients, as measured by the Behavioral Rating Scale and the Multidimensional Scale. Results of the Weekly Rating Scale were charted. They were manifestly in favor of the demonstration patients. The brief psychomotor tests of efficiency failed to differentiate demonstration from control patients during this experimental interval, but cooperative responses on these tests were too few to permit statistical tests of significance.

Qualitative aspects of the experiment and its results were discussed. This demonstration program constituted a stimulating training device. 14 references. 1 figure. 5 tables.—*Author's abstract.*

43. *The Neurasthenic Psychopath.* W. L. TONGE, Cheshire, England. Brit. M. J. *4921*:1066–1068, April 30, 1955.

This paper is a clinical report on an outpatient clinic for a group of unemployed men with psychiatric disabilities. Attention is drawn to the profound degree of inadequacy that many of these patients exhibited in all aspects of their lives and which was apparent also at interview. On topics that one would suppose would awaken their self-interest, their talk became vague. Their complaints and dissatisfactions, their present difficulties and previous happiness, and their habits and fears for the future would arouse no definite affect or point of view that could be seized upon and discussed. A striking feature was their tolerance of worsened conditions and their apparent ability not only to obtain satisfaction from these conditions, but even to desire them.

Attendance at the clinic did not improve these patients' health or their work record. Compared with a similar survey made in 1935, it was noted that gross hysteric phenomena were not as prevalent in the present survey.

It was pointed out that such character disorders are not often described in the literature because such patients are only referred to a doctor under special circumstances where administrative authority seeks medical advice regarding their disposal.

It was concluded that most of these cases would remain a charge of the social and welfare services, with little hope of truly successful rehabilitation. 9 references.—*Author's abstract.*

## GERIATRICS

44. *Orientation in Geriatric Psychiatry.* RAPHAEL GINZBERG, Tomah, Wis. J. Am. Geriatrics Soc. *3*:435–438, July, 1955.

The present-day stand of geriatric psychiatry can best be described as in a state of transition. There is an awareness that custodial care is not an answer to the problems. However, future developments appear to be vague and uncertain. As in any state of transition, observations made are contradictory, concepts are still rooted in the static approach of the past, and few practices are influenced by dynamic ideas of contemporary psychiatry.

The elderly psychotic's behavior, particularly his impaired verbalization, makes contact with him very difficult. There is therefore a tendency to classify him as hopeless and to abandon further exploration of his condition. Consequently his conflicts, disappointments, and frustrations are generally overlooked and their dynamics not recognized. Unfortunately, many heterogeneous factors make the use of new principles in geriatric psychiatry difficult. A few of these factors are: (1) failure of the existing diagnostic nomenclature to provide sufficient information about the actual mental condition of the patient; (2) retardation of the introduction of new methods because of the absence of standard procedures based on modern principles; (3) lack of trained personnel and an insufficient number of psychologists and psychiatrists assigned to geriatric wards, which makes any systematic work extremely difficult; and (4) lack of interest in geriatric psychiatry on the part of experienced psychiatrists as well as residents and/or trainees. Such indifference is a serious handicap to further developments. Nevertheless, in spite of many handicaps, the atmosphere of hopelessness typical of the past is in process of changing. The era of psychologic indifference and of therapeutic inertia is over.—*Author's abstract.*

## PSYCHIATRY AND GENERAL MEDICINE

45. *The Relationship of Endogenous Psychoses to Physical Illnesses (Über Beziehungen endogener Psychosen zu koeperlichen Krankheiten).* ULRICH SPIEGELBERG, Hamburg-Eppendorf, Germany. Fortschr. d. Neurol., Psychiat. *6*:221–248, June, 1955.

The author describes 9 cases of endogenous psychoses in which physical illnesses (gastric or duodenal ulcer, bronchial asthma, urticaria) or characteristic somatic complexes (angina pectoris, renal colic) appeared in a definite time relationship to the development of psychotic manifestations.

In 1 case the patient suffered for 12 years from repeated gastric and duodenal ulcers. This was followed by a period of 11 years, in the course of which he had three attacks of depression but no gastrointestinal symptoms. Then he developed a jejunal ulcer requiring operative intervention, but he was free of psychotic manifestations.

Another patient had three depressive attacks. The first two started with cardiac complaints in the nature of angina pectoris. Between the two periods of depression he suffered from gastric ulcer while free of mental symptoms. The third attack apparently followed four days after an anginal attack that produced a myocardial infarction.

The author reviews the literature pertaining to the subject of his paper rather extensively. Reference is made to writers in the field of internal medicine, psychosomatic medicine, and psychiatry who reported cases (asthma, ulcer, urticaria, etc.) that showed an apparent relationship between the somatic and psychopathologic manifestations.

Based on his own case material and the literature, the author observed the following chronologic combinations: (1) alternating short and long phases of somatic and psychotic symptomatology; (2) synchronous appearance of both manifestations; (3) appearance of certain physiologic reactions (such as angina pectoris, myocardial infarction, or renal colic) at the onset of a psychotic phase or attack.

The author, in reporting the literature, avoids making any interpretations. He also does

not discuss any dynamics that might be operative in his cases or in those mentioned in the literature. He favors the view that the psychotic reaction neither causes nor eliminates the somatic condition or vice versa, but that a third factor is responsible for both. He suggests a working hypothesis based on Hansen's views that there is a relationship between allergic reactions having a phasic course involving the vegetative system, on the one hand, and manic-depressive reactions, on the other.

The author emphasizes the need for further experimental, statistical, heredobiologic, and clinical studies in regard to the connection of psychoses to other illnesses with objective physical changes.

The attitude of the author is best clarified in his closing suggestions to approach: (1) the problem of the psychoses from the viewpoint of the internist and psychotherapist, and (2) the psychopathology of physical illness in a psychosomatic framework.—*E. H. Friedman.*

46. *The General Practitioner and the Discharged Mental Hospital Patient.* KENNETH E. APPEL AND ALBERT SCHEFLEN, Philadelphia, Pa. J.A.M.A. *159*:1278–1282, Nov. 26, 1955.

About 250,000 discharged mental patients return to the community each year badly in need of help in readjustment. Many will come to the general practitioner.

The physician needs to know some basic psychiatry. He needs to understand the conflicts and assets of the patient and the positive and negative influences of the family and the community. Last, the physician needs to understand himself, including his own prejudices, areas of anxiety, and tendency to overidentify with the patient or with the family against the patient.

The physician is the guardian of both the patient and the community. The patient needs support in many undertakings and protection from self-defeating tendencies. The community cannot be exposed to dangerous patients. The doctor must weigh the factors. The calculated risk is part of medical practice, and there is a tendency to recommit the patient who causes anxiety. We need to differentiate real maturation from antisocial behavior and not too quickly stifle growth in a patient by hasty condemnation or rehospitalization.

The failure to take physical complaints seriously in a mental patient seems to be a common mistake. Psychosomatic syndromes, however, are common in patients during readjustment to the community.

The physician has many therapeutic approaches available, such as support, reassurance, acceptance, relief of anxiety, aiding in the development of potential talents and human relationships, abreaction of strong feelings, mediation in social reintegration—*Author's abstract.*

## PSYCHIATRIC NURSING, SOCIAL WORK, AND MENTAL HYGIENE

47. *Towards an Operational Definition of Religion.* SAMUEL GLASNER, Baltimore, Md. Internat. Rec. Med. & G. P. C. *168*:778–782, December, 1955.

The scientific study of religion often suffers from semantic confusion. Even the usual dictionary definitions of religion are unsatisfactory because they are dominated by the

concepts prevalent in our Western culture. Objective analysis of a great many different religions suggests that the one element that they all have in common is not the worship of a Deity or concern with the superhuman or supernatural. If we apply the operational approach to our study of religions, we discover that they all seem to deal with the individual's orientation toward himself and toward the universe. From an operational standpoint, therefore, religion may be defined as man's attempt to answer the question "Who am I?" and the corollary question "What am I doing here?"

As we examine the various ways in which different religions have attempted to answer this question, we seem to discern three fairly distinct patterns: the static self, in which the self occupies the central portion in the universe; the contracting self, which retreats from the universe and looks within the self for all truth and reality; and the expanding self, which develops an ever widening identification with the universe.

From the standpoint of psychotherapy, the understanding of religion in this light becomes extremely significant. Many of the personality problems that disturb the psychiatrist's patients and the counselor's clients are seen to be fundamentally religious in nature. The psychotherapeutic goal would then become a means to help the individual "find himself" religiously, or clarify his own basic pattern of orientation or "life-style," and discover how this may function most satisfactorily within the society in which he lives. 3 figures.—*Author's abstract.*

48. *The Psyche and the Symbols of Religion.* M. ESTHER HARDING, New York, N. Y. Internat. Rec. Med. & G. P. C. *168*:749–753, December, 1955.

Conflicts underlying neurotic and psychic disturbances are frequently concerned with the lack of a satisfactory spiritual life, due to the neglect of those values that transcend personal considerations. Religions are based on the experience of such values, which have a powerful and fascinating quality. But if the teachings of religion no longer satisfy the psychologic needs of the individual and he turns to explore the unconscious by the method known as analytical psychology, introduced by C. G. Jung, he will first encounter the problems of the personal unconscious, with which the freudian technique is largely concerned; and, having dealt with these layers, he will begin to experience the dominants of the collective unconscious, which is common to all mankind. Among these are those archetypes on which religions of all times have been based.

Examples of dreams containing symbols that have the quality of awe and fascination characteristic of the "numinous" or transpersonal realm are given. Such experiences affect the life of the individual profoundly. They may have a healing effect on the body and on the neurosis, and they surely result in a healing of the soul, with a release from conflict and guilt.

The spiritual problems of human beings may be met either by teaching the doctrines and practices of religion, or they may be approached from a diametrically opposite position: namely, by examining what actually lies within the depths of the psyche, where there will be found symbols of the supreme value in a guise that meets the individual's need and that will lead him aright, no matter how strange they may seem from the viewpoint of orthodox religion.—*Author's abstract.*

49. *Psychiatric Thought in Chinese Medicine.* ILZA VEITH, Chicago, Ill. J. Hist. Med. & Allied Sc. *10*:261–268, July, 1955.

Psychiatry, in the Western sense of the word, has neither developed in China nor did it take hold after it was introduced there from the West. The first mental hospital, accommodating 30 patients, was opened in 1897, in Canton, and grew into a 500 bed institution. The total number of psychiatric beds for a population of more than 500 million Chinese has rarely exceeded 1200, and most of the mental hospitals of China terminated their existence during the Pacific War.

There exists a general belief that the Chinese are self-restrained and phlegmatic, and that they exhibit a remarkably stable state of mental health. It is of interest to study the earlier Chinese medical literature for traces of indigenous thought on mental health and also to examine the structure of traditional Chinese society in an attempt to discover the reasons for the failure of psychiatry to find a place among such a large part of the world's population.

Chinese medical literature reveals an early awareness of the mind-body relationship and a profound understanding of what is now called psychosomatic medicine. According to the oldest Chinese medical writings, any disease, but particularly mental disorder, was caused by an imbalance of the two primary forces in man: the *Yin* and the *Yang*. These two forces stand for the negative and the positive, the dark and the light, the moon and the sun, the noxious and the beneficial, and the male and female elements present in both man and woman. In essence the *Yin* and the *Yang* represent a bipolarity, or a dual force, assumed by the Chinese to be everywhere in nature. A mental disorder results from an imbalance of the *Yin* and the *Yang*, and the ancient Chinese believed that this was caused by the individual himself, who had committed a moral transgression, by deviating from the *Tao*.

A further ethical and social principle, deeply ingrained in the Chinese personality, is that of filial piety. This has resulted in a rigid, life-long obedience to the family hierarchy and the family honor and must have imposed a severe psychologic strain on many individuals. But as long as it was the standard of behavior it was accepted without question. It was, and still is accompanied by the concept of *Lien*, or "face." We are familiar with the idea of losing face, but this does not have the profound effects upon the individual that it does among the Chinese, with whom *Lien* is both a social sanction for enforcing moral standards and an internalized sanction. On the other hand, the concept of sin, which has played an important part in Western culture, is foreign to the Chinese.

The intricacies of these guiding principles are conducive to highly circumspect behavior, and in many respects the concept of "face" removes frictions from interpersonal relationships that have tested the sensitivities of Western behavior. Moreover, without the concept of sin and without the tradition of vengeful deities smiting mortals with the curse of madness, mental disease was never associated with religious guilt, nor was it apt to be the cause of family disgrace.

Regardless of the underlying reasons, it seems clear that Western observation on the relative stability of Chinese mental health contains more than a grain of truth, even though statistically valid criteria are not available. It also appears that, far from being the result of specific racial qualities, this apparent stability is closely linked with the ancient ethical and social precepts of the Chinese. 20 references.—*Author's abstract.*

50. *Contributions of Psychiatric Social Work to Direct Treatment of Psychotic Patients.* EMMA M. KENT AND FANNY HOUTZ, Denver, Colo. Am. J. Orthopsychiat. *25*:127–137, January, 1955.

In the acute psychiatric service of a general hospital, all resources must be used to return those patients to the community who have the potentialities for making an adjustment. Utilizing the special skills of the psychiatric caseworker in establishing helpful relationships with patients has been found to be an important means to that end. Contrary to popular supposition, casework treatment of psychotic patients is possible and rewarding.

The casework relationship often begins with concrete service to the patient who suddenly finds himself cut off from the outside world and from the material possessions in which he has found some security. Dealing with the anxiety of the patient and his relatives regarding the hospitalization helps to strengthen the healthy ties between the patient and his family. Social history material and any necessary legal papers are obtained.

While the patient is in the hospital, the caseworker encourages the development of a meaningful interpersonal relationship that is both accepting and realistic. This relationship is supplementary and complementary to that of the psychiatrist and varies with the individual needs of the patient. Since the psychotic patient suffers from a severe deficiency in satisfactory human contacts, this gives him an additional opportunity for a constructive experience and helps in his day to day adjustment on the ward.

The caseworker helps the patient's transition from the hospital to outside life with direct planning and by participating with the rest of the staff in dealing with the patient's separation anxiety. The result of this activity is a firm foundation for a continuing relationship which the patient can use during follow-up care, and for a resource in the event of future emergency. 5 references.—*Author's abstract.*

*For Reference*

51. *The Scope of Nursing Today.* L. FREY. Nursing Outlook *3*:152–155, March, 1955.

52. *The Epidemiological Study of Mental Illness and Mental Health.* P. V. LEMKAU. Am. J. Psychiat. *111*:801–809, May, 1955.

## PSYCHOLOGIC METHODS

53. *The Scientific Status of Mental Measurement.* F. W. WARBURTON, Manchester, England. Brit. J. Psychol. *61*:122–129, May, 1955.

This paper is largely concerned with the fields of mental measurement and personality testing. Certain factors making for variability of performance in different investigations are considered.

Two common criticisms of mental testing based on the theory of measurement are (a) that if measurement is used in psychology it should be in terms of linear units, which are constant in size, whereas mental tests are scored in terms of items of different difficulty, and (b) that there is no true zero in mental measurement so that it is impossible to use ratios: the state-

ment, for example, that one person is twice as intelligent as another has no meaning.

The variables used by the applied psychologist are multidimensional. It is difficult to think of any human characteristic from religious conversion to the knee jerk that is not multidimensional, and this limitation has to be accepted. We also have to accept the fact that human behavior, at the level studied by the psychologist, fluctuates from occasion to occasion. It often happens, for example, that a person is, according to examination results, a good mathematician one day and a poor one the next, an introvert at breakfast and an extrovert at dinner; his performance in the high jump may fluctuate within a single minute. This variability extends over the whole range of behavior, and is unavoidable.

Another line of criticism of the methods of measurement used in mental testing is derived from the holistic point of view, that to take over the mathematical methods of the physical sciences and to use them for the purpose of psychologic description and analysis commits us to a fundamental flaw. We cannot add units of ability as we add 12 inches to make a foot. Yet the limitations of analytic methods are common to science. In order to understand any situation, we analyze it into elements and study the separate elements in isolation. When the isolated elements are recombined, something is missing in the reconstructed situation that was present in the original situation. Physical bodies are incompletely analyzed into electrons and protons, and water is described, rather absurdly, as the combination of two gases. This difficulty is not peculiar to psychology and is particularly marked if the subject matter is as complex as human behavior. 5 references. 2 tables.—*Author's abstract.*

54. *Neurologic Techniques and Rorschach Test in Detecting Brain Pathology.* JEROME FISHER AND THOMAS A. GONDA, San Francisco, Calif. A. M. A. Arch. Neurol. & Psychiat. *74*:117–124, August, 1955.

This study compares the validities of standard neurologic techniques with the validity of a Rorschach sign method (Piotrowski) in the diagnosis of brain disease.

The sample consists of 118 patients, all of whom were admitted to the neurology ward of a Veterans Hospital with various complaints and symptoms referable to the nervous system. All patients received thorough neurologic work-ups, including electroencephalograms, skull roentgenograms, and lumbar punctures. In addition, a Rorschach test was administered to each patient as part of a psychologic examination. Diagnostic procedures, such as pneumoencephalography, were performed as indicated.

The criterion groups were derived as follows. Two attending neurologists independently studied the completed hospital charts of the 118 patients. In addition, all cases were examined in consultation by one or the other of them. They judged 84 patients as having pathology above the foramen magnum and the remaining 34 patients as presumably having no such pathology. The groups were found to be comparable in age, intelligence, education, and socioeconomic status. An index of reliability of 0.93 indicated a high agreement between the two neurologists and the pooled ratings of many comparable neurologists.

This investigation differs from previous research on brain pathology in that there was obtained (1) greater representativeness to actual practice through the selection of cases from a general hospital neurology ward, yielding a continuum of cases from extreme through borderline to no brain pathology; (2) differentiation between the group with brain pathology

and the control group on the basis of intensive neurologic work-up rather than of psychiatric diagnosis; and (3) a measure of reliability of the criterion.

The validity coefficients ($\phi$) show that of the six diagnostic procedures studied, the Rorschach method discriminates very reliably between the organic and the nonorganic groups. The electroencephalogram, the neurologic examination, and the lumbar puncture also differentiate significantly between the groups. The skull roentgenograms and pneumoencephalograms, however, fail to demonstrate stable differences.

In addition, the findings indicate that high call rates of brain damage are characteristic of the neurologic examination, 63 per cent, and the electroencephalogram, 62 per cent; they err mainly in the direction of calling almost 40 per cent of the nonorganic cases organic. On the other hand, the Rorschach method, lumbar puncture, and skull roentgenograms call fewer organic cases, 29 per cent, 21 per cent, and 16 per cent, respectively, and their errors are reflected in higher percentages of false negatives. However, the number of false positives for these techniques is remarkably low. They reveal a high tool accuracy, 94 per cent, 95 per cent, and 88 per cent, respectively, when they call a case organic. Because the criterion was based in part upon the neurologic techniques, and not upon the Rorschach method, the findings show that as an isolated procedure, the Rorschach is superior to the best of the individual neurologic techniques in detecting the presence of brain disease and, therefore, warrants inclusion among the diagnostic consultative procedures of the clinical neurologist.

There are some interesting applied and theoretic implications in this study. Clinical neurologists and other medical specialists tend to disregard a negative finding in an individual case if, in their opinion, this finding opposes the patient's history, presenting complaints, symptoms, and other diagnostic data. A positive finding, however, is regarded with considerable respect, provided the diagnostic technique is accurate in at least 80 per cent of the cases. In the instance of a negative finding, the physician usually functions with a realistic tolerance for error and clinical relativism. We can understand this from our data, for we observed that there are relatively large numbers of false negatives in five currently used standard neurologic procedures. In the case of a positive call by the Rorschach test, i.e., when five or more Piotrowski signs are present, the Rorschach test demonstrates a 94 per cent accuracy; when there are four or less signs, the finding is inconclusive because of the large number of false negatives.

From the results of our study, we may assume that the errors in the diagnostic tools themselves play a part in the yield of false negatives. We suspect, however, that there may be biologic factors in operation that our diagnostic techniques cannot take into account at this stage of our knowledge. Our hypothesis is that when pathology is present in the adaptive human organism, homeostatic mechanisms are involved actively and continuously to compensate in ways that seek to restore the organism to its former state. This on-going process may account for "normal" responses (false negatives) to our tools in spite of the presence of pathology. Our techniques seem to have been devised so as to assess pathology in status, i.e., when adaptiveness has been curtailed beyond a certain point. Perhaps, in addition, we need to devise other diagnostic procedures that could see through the camouflage of compensatory mechanisms by which the adaptive organism constantly strives

toward re-establishment of its natural state and ultimate continuation of its survival. 5 references. 6 tables.—*Author's abstract.*

*For Reference*

55. *A Normative Social Adjustment Scale.* PAUL BARRABEE, EDNA L. BARRABEE, AND JACOB E. FINESINGER, Boston, Mass., and Baltimore, Md. Am. J. Psychiat. *112*:252–259, October, 1955.

## TREATMENT

### a. General Psychiatric Therapy

56. *An Approach to the Treatment of Massive Mental Hospital Populations.* JOHN T. ROWELL, Milledgeville, Ga. Ment. Hyg. *39*:622–630, October, 1955.

Milledgeville State Hospital has more than 11,000 patients in residence, with at present only a limited staff available to provide them with active care. There is a recognized need for some approach that will give the maximum benefit to these patients by using this limited staff efficiently. This study was undertaken to determine the effect of a ward activation program on the highly regressed patient.

Two wards with similar patient and personnel characteristics were used for this experiment. The building psychologist, acting as project director and therapist, introduced a total activational program on the experimental ward, utilizing the cooperation of the ward physician, attendants, and occupational and recreational therapists. These activities were directed toward increasing patient interaction. Activities included group psychotherapy, reading and music therapy, games, special occupational and recreational therapy projects, and ward improvements.

After six months of concentrated effort, 8 patients were furloughed from the experimental ward in contrast to only 1 from the control ward. In addition, 3 experimental patients showed marked improvement and 1 showed slight improvement. The general level of the experimental ward was raised while little change was observed in the control ward. 4 references.—*Author's abstract.*

### b. Drug Therapies

57. *Experimental Psychiatry. IV. Hallucinogens: Tools in Experimental Psychiatry.* MAX RINKEL, ROBERT W. HYDE, AND HARRY C. SOLOMON, Boston, Mass. Dis. Nerv. System. *16*:229–232, August, 1955.

Hallucinogen is the name that Hoffer, Osmond, and Smythies gave to a group of chemicals that contain the indole ring in their molecular structure and cause hallucinations. Of the chemically identified compounds, the diethylamide of *d*-lysergic acid (LSD) of the Sandoz Chemical Works in Basel, Switzerland, and synthetic mescaline have been most widely used in recent years. Both chemicals have in common the fact that they produce psychotic-like phenomena in normal people. Therefore, these chemicals have been used as tools for the

production of experimental psychosis of which clinical as well as physiochemical phenomena could be studied. The result of these studies brought the problem of psychosis once again into the focus of biochemical considerations. The authors, on the basis of their own experimentations with LSD and of observations reported in the literature, arrived at the conclusion that a disturbance in the adrenal cycle, possibly the endogenous production of a noxious metabolite, may play an important part in the development of psychoses. The authors stress the necessity of relating the various observations in a consistent theory and point up the need of further careful experimentation for which hallucinogens have proved themselves to be effective tools. 18 references.—*Author's abstract.*

58. *Critical Study of 150 Cases of Sleep Treatment (Étude critique de 150 cas de cure de sommeil).* P. SIVADON AND C. FORZY. Ann. méd.-psychol. *113*:433–438, March, 1955.

The methods of treatment employed in the series of cases reported were of three types: (1) deep sleep, in which patients were kept asleep for 16 to 20 hours daily, for a period of 15 or 20 days; sometimes two courses of treatment were used: deep sleep for 10 days, then an interval of 4 to 10 days, then another course of treatment for 10 days; (2) prolonged partial sleep, in which patients were kept active (gymnastics or occupational therapy) for part of the day and under sleep treatment for the rest of the day, used chiefly in schizophrenics; and (3) sleep treatment for two to six days in agitated patients, which resulted in the relief of the agitation. One drug commonly used to induce sleep was eunoctal, which was given by intravenous injection (0.50 Gm.); other drugs employed were Largactil, Phenergan, and a barbiturate, which were given by mouth or in suppositories. Of the patients treated, 45 showed marked and permanent improvement, including 10 of 51 schizophrenics, 4 of 6 patients with mental confusion, 18 of 19 patients with depression syndromes, and 8 of 9 patients with chronic hallucinations and delirium. In 13 cases the treatment was stopped because of the patient's opposition; this included 5 cases in which a second course of treatment was attempted. A less marked degree of permanent improvement was obtained in 13 of the patients treated, and definite but temporary improvement was obtained in 47 patients. 1 table.

59. *Spectacular Therapeutic Results with Chlorpromazine in Severe Psychoses with a Special Dosage Schedule without Other Drugs (Sur une série de résultats thérapeutiques spectaculaires per la chlorpromazine dans des psychoses graves suivant une posologie particulière sans association médicamenteuse).* H. BARUK, J. LAUNAY, AND J. BERGÉS. Ann. méd-psychol. *113*:442–448, March, 1955.

In the cases reported the following dosage schedule of chlorpromazine was used: 50 drops in two divided doses daily for four days, then 100 drops in two divided doses for six days. During this period, the patient is carefully observed to determine the behavior reactions and also the physiologic reactions, the pulse rate being recorded twice daily and the temperature once daily. The treatment is continued by increasing the amount of chlorpromazine given by mouth up to 200 drops daily in two divided doses, or by changing to intramuscular injections, giving 50 mg. daily at first, and if necessary increasing to two injections of 50 mg. each daily; as the injections may be painful, 2 cc. of procaine may be added and sometimes an ampule of liver extract, as this seems to favor diffusion of the drug and also to diminish

its toxicity for the liver. Throughout the period of treatment certain precautions must be observed, including recording the pulse rate twice a day, making repeated blood examinations, and taking blood pressure records three times a week. The patient should be kept in bed for at least two and one-half hours after each administration of the drug. The relatively small dosage of chlorpromazine used is intended as a sedative and not a narcotic treatment. The duration of treatment depends on the rapidity with which the desired results are obtained.

Of 9 cases with mania, 8 were relieved and returned to normal in a few weeks of treatment; in 1 case the maniacal phase was followed by depression. In 12 cases of melancholia, 6 were entirely relieved by one or several treatments with chlorpromazine, 5 were greatly improved, except for the persistence of some degree of anxiety, and 1 is still under treatment. In 4 cases of manic-depressive syndrome, after repeated treatments in both phases of the syndrome, very satisfactory results were obtained in 2 cases and definite improvement in the other 2 cases. In 4 cases of hallucination with delirium, good results were obtained in 2 cases, but prolonged treatments or repeated courses of treatment are indicated in this type of case. In 5 cases of catatonia, good results were obtained in 2 cases; the other 3 patients did not respond to the treatment. In the 35 cases of schizophrenia treated, good results were also obtained, but in some cases the improvement was not maintained after varying periods of time; in some cases of hebephrenia, the results were remarkably good. Two illustrative cases are reported.

### c. Psychotherapy

60. *How Important Is Psychotherapy to the Hospitalized Psychiatric Patient?* BERNARD A. STOTSKY, Brockton, Mass. J. Clin. Psychol. *12*:32–36, January, 1956.

Psychotherapy, consisting of a series of verbal communications between a therapist and a patient, involves the ability to utilize words as a medium for expressing emotions. Since middle class patients are more verbal than lower class patients, psychotherapy should be more suitable for middle class patients. In practice we find that persons from lower socioeconomic groups rarely come to psychotherapy voluntarily, communicate poorly with therapists, and resist attempts to relate physical symptoms to emotional problems.

In this study a predominantly lower class sample of 60 neuropsychiatric patients at a Veterans Administration hospital and 30 normal patients were surveyed to assess attitudes toward psychotherapy. Two types of data were secured: (a) an activities preference questionnaire designed to measure relative preferences for 12 rehabilitation and therapeutic activities and (b) responses to structured and unstructured questions relating to activities and modes of treatment regarded as contributing to improvement in their illnesses. Psychotherapy as an activity was preferred less than manually oriented rehabilitation activities and various forms of recreation. Moreover, psychotherapy was regarded by the patients as less significant than rehabilitation activities in bringing about improvement. Only 23 per cent of patients undergoing psychotherapy spontaneously mentioned it as contributing to their getting well. Degree of preference for psychotherapy was unrelated to occupation or to severity of illness. Patients with middle class backgrounds showed a significantly greater preference for psychotherapy than those from lower class backgrounds. With respect to ac-

tivity preferences, patients and normals were similar, both rejecting psychotherapy and other primarily verbal activities.

The findings suggest the desirability of modifying present techniques of psychotherapy or developing new ones to make them more applicable to less verbal, more motorically oriented lower class psychiatric patients. Such techniques should be integrated with rehabilitational, recreational, and work-centered activities to make them more meaningful to these patients. 6 references. 2 tables.—*Author's abstract.*

61. *Religion and Psychotherapy: Practical Aspects.* LAWSON G. LOWREY, New York, N. Y. Internat. Rec. Med. & G. P. C. *168*:783–785, December, 1955.

A much condensed account of the actual process and goals in psychotherapy is given, and the roles of patient and therapist are briefly outlined. The major goal is integration or reintegration, as the case may be, of the patient's personality. This is to permit bringing disturbing unconscious conflicts and complexes, complicated by unpleasant and unacceptable emotions and drives, into the consciousness where they can be effectively dealt with in terms of present realities, rather than interfering with needed and appropriate realities.

Psychotherapy, pastoral counseling, and the confessional are briefly compared, the differences and one major similarity (the relief of guilt) being clearly brought out. Finally, an essential similarity in ideals and goals of religion and psychotherapy is brought out, even though methods are different and the ideologies often seem to clash.—*Author's abstract.*

62. *Value Systems in the Psychotherapeutic Process.* WARNER L. LOWE, New York, N. Y. Internat. Rec. Med. & G. P. C. *168*:786–789, December, 1955.

The article discusses first the implications of a study by Werner Wolff, "Facts and Value in Psychotherapy" (Am. J. Psychotherapy *8*:466, 1954). The question raised is why the value factor can have the lowest place among therapists' goals while a majority realizes that it has a possibly decisive influence upon the patient's ultimate adjustment.

In contemporary psychiatric and psychologic literature, there appears a clear trend toward the use of eclectic techniques and a definite preference for directive and relationship therapies that emphasize ego roles and social factors. The goal of such therapies is discussed. The question is raised as to the role of the therapist in the therapeutic process. The latter is characterized as the reshaping of the patient's perception and ego functions under the impact of the therapist-patient relationship and the therapist's interpretations. The goal is characterized as the emergence of moral values and the replacement of egocentric preoccupation by social participation and social responsibility.

Value systems of theology and psychology are compared, and brief case histories are presented illustrating similarities and differences in means and goals.

Personality factors in the psychotherapist are elucidated, and efforts leading beyond mere psychoanalysis toward psychosynthesis are discussed. The need for and the value of a "poor man's psychiatry," to be practiced by trained nonpsychiatrists, is demonstrated.

The ultimate goal of psychotherapy is described in terms of the self-realization of the individual as the result of his exposure to the consistent value system of the mature, ethical, and socialized therapist. 8 references.—*Author's abstract.*

# neurology

## CLINICAL NEUROLOGY

63. *Neurologic Manifestations in Collagen Diseases.* GILBERT H. GLASER, New Haven, Conn. Neurology *5*:751–766, November, 1955.

The modern morphologic concept of these disorders of connective tissue includes acute lupus erythematosus, polymyositis or dermatomyositis, scleroderma, periarteritis nodosa, rheumatoid arthritis, and rheumatic fever. This paper is concerned with all but the latter two conditions. Overt neurologic signs and symptoms occur in these diseases due to both diffuse and focal lesions of the nervous system, especially secondary to involvement of the smaller blood vessels. These produce focal and generalized seizures, aphasia, muscle weakness, cranial and peripheral nerve defects, electroencephalographic changes, organic mental deficiencies, and abnormalities of the cerebrospinal fluid protein. There is occasionally a lack of clinical and pathologic correlation in that extensive lesions may exist asymptomatically. The course and prognosis of these disorders are extremely variable and uncertain. Spontaneous remissions and exacerbations occur even in acute lupus and periarteritis nodosa, although the mortality is high. Generally, neurologic disturbances appear during a very active phase, especially preterminally.

The methods and results of acute and long-term treatment, especially with the hormones cortisone and ACTH, are presented in relation to both the general disorder and the neurologic manifestations. It is emphasized that this treatment is mainly suppressive but may prolong the course. The hormones induce the profound metabolic and systemic changes of the hyperadrenal state of Cushing's syndrome and must be administered with great care. The problems concerning the occurrence of complications such as seizures, abnormal mental states, and asthenia are reviewed with regard to mechanisms of production, diagnosis, and considerations concerning continued therapy. 62 references. 1 table.—*Author's abstract.*

64. *Hereditary Combined Neurinomas and Meningiomas.* LEO M. DAVIDOFF AND JOHN MARTIN, New York, N. Y., and Washington, D. C. J. Neurosurg. *12*:375–384, July, 1955.

While the hereditary character of von Recklinghausen's disease is well known, the combination of multiple neurinomas and meningiomas of the nervous system, which is a rare combination in the first place, is even more unusual in hereditary form. The authors have had the privilege of studying the case of a father and daughter both suffering from combined multiple neurinomas and meningiomas. One of the authors of the present contribution had participated in the treatment of the father. He had already been dead some years when his 15 year old daughter first presented herself to one of us with the symptoms of spinal cord disease that proved to be due to a meningioma. This is an unusual lesion for a 15 year old girl, and her course postoperatively was followed with the greatest interest. She was well until she was 21 years of age, when she developed signs of increased intracranial pressure and a bilateral cerebellopontine angle syndrome. During the operation, posterior fossa

meningiomas were disclosed. She eventually died, and at the postmortem examination multiple meningiomas and neurinomas were found. 2 references. 6 figures.—*Author's abstract.*

## ANATOMY AND PHYSIOLOGY OF THE NERVOUS SYSTEM

65. *Prostigmine-responsiveness and the Diagnosis of Myasthenia Gravis.* LEWIS P. ROWLAND, New York, N. Y. Neurology *5*:612–624, September, 1955.

Case histories are described to illustrate some of the problems involved in the clinical definition of myasthenia gravis: a woman who appeared to have myasthenia gravis but who never responded to neostigmine or other cholinergic drugs; a baby with presumptive neonatal myasthenia who showed no clear-cut response to neostigmine; cases with temporary lack of response to neostigmine but typical response later; a case with several atypical features, some suggesting lupus erythematosus; a patient with severe myocarditis and polymyositis; and cases in which the diagnosis was uncertain without the use of curare or quinine.

Any syndrome of muscular weakness, not accompanied by alteration of tendon reflexes or sensation, in which strength improves significantly and unequivocally after the administration of adequate amounts of neostigmine or (3-hydroxyphenyl) dimethylethylammonium bromide, should be considered to be myasthenia gravis, except when psychoneurosis can be demonstrated to be etiologically important. The presence of inflammatory lesions in skeletal muscle, atrophy of skeletal muscle, or thyrotoxicosis does not automatically change the diagnosis from myasthenia to polymyositis, muscular dystrophy, or thyrotoxic myopathy. Although some features may suggest these alternative diagnoses, it may be least confusing to regard any neostigmine-responsive syndrome as myasthenia and to recognize that myasthenia may occur in association with other disorders.

The converse of this postulate is not necessarily true, since some patients with a clinical syndrome identical with that described for myasthenia gravis may never respond to neostigmine in diagnostic fashion. Such cases create a problem in understanding those cases of polymyositis and weakness associated with hyperthyroidism which do not respond to neostigmine. 41 references. 6 figures.—*Author's abstract.*

## CEREBROSPINAL FLUID

66. *The Blood-Cerebrospinal Fluid Barrier in Tuberculous Meningitis and Allied Conditions.* H. V. SMITH, L. M. TAYLOR, AND G. HUNTER, Oxford, England. J. Neurol., Neurosurg. & Psychiat. *18*:237–249, November, 1955.

This study is concerned with the passage of substances from blood–C.S.F., i.e., the blood–C.S.F. barrier, the principal substance studied being sodium bromide. The validity of the bromide test as a measure of the permeability of the blood–C.S.F. barrier has now

been demonstrated, and results are expressed as the "bromide ratio"—that is to say, bromide per unit volume serum bromide per unit volume C.S.F. In subjects without overt disease of the nervous system, the bromide ratio at equilibrium varies between 1.95 and 3.39 with a mean of 2.6. The test has been used extensively in cases of tuberculous meningitis and also in the experimental intrathecal tuberculin reaction. By the latter is meant the wave of sterile meningitis that follows the introduction of tuberculin into the C.S.F. of someone sensitized to tuberculin, and in its complete form is diphasic and consists of an initial wave of pleocytosis, which is predominantly polymorphonuclear and is accompanied by an abrupt rise in protein content of the C.S.F. This is maximal about 24 hours after injection. The second phase is maximal between the fifth and eighth days of the reaction and is a lymphocytic pleocytosis usually accompanied by a second peak in the protein curve.

The bromide test was used to demonstrate the profound effect on the blood-C.S.F. barrier exerted by tuberculin, when this is introduced into the C.S.F. of a sensitized subject. When the experimental intrathecal reaction is fully developed, the blood-C.S.F. barrier is abolished to bromide, and is impaired to penicillin also.

There is no quantitative relationship between the intensity of the inflammation of the meninges, as judged by the height of the pleocytosis and protein control of the C.S.F., and the depression of the barrier.

It was also shown that both Benadryl and, to a greater extent, cortisone are capable of modifying the intrathecal tuberculin reaction, and in such abortive reactions, the barrier to bromide is still seriously impaired, but is restored more rapidly than after a complete reaction. Cortisone and Benadryl appear to be antagonistic to tuberculin in the effect on the blood-C.S.F. barrier.

The test has proved useful in the diagnosis and management of tuberculous meningitis. The effect of tuberculous meningitis on the blood-C.S.F. barrier to bromide is identical with that of the experimental intrathecal tuberculin reaction. The ratio remains low as long as the infection is active, but the barrier to bromide is gradually restored as the active meningeal infection is controlled. Of 45 cases of tuberculous meningitis in whom the test was carried out during the first month of illness, the ratio was less than 1.3 in 37, and in 18 it was less than unity, while in only 3 did it exceed 1.6. A ratio of 2.0 or higher has now been found in 25 cases at a time when on clinical grounds the infection was thought to be obsolete; none have shown evidence of relapse, but the follow-up record is too short for the restoration of the blood-C.S.F. barrier to bromide to be accepted as a criterion of cure.

Studies of the bromide ratio for ventricular (S/V), cisternal (S/C), and lumbar (S/L) C.S.F. show that the relationship $S/V > S/C > S/L$ is invariable. In active tuberculous meningitis, all 3 ratios are depressed but their relationship is never reversed.

It is shown that the effect of meningeal inflammation on the blood-C.S.F. barrier varies with the etiology of the inflammation and with respect to different substances, and it is suggested that the marked depression of the barrier is in some way a function of the hypersensitive response as such, and that in those varieties of meningitis in which the barrier is little affected, some mechanism other than antibody-antigen reaction is responsible for the inflammation. 24 references. 6 figures. 7 tables.—*Author's abstract.*

## CONVULSIVE DISORDERS

67. *Progressive Familial Myoclonic Epilepsy in Three Families: Its Clinical Features and Pathological Basis.* D. G. F. HARRIMAN AND J. H. D. MILLAR, Belfast, Ireland. Brain *78*:325–349, 1955.

This paper records the clinical features of 8 cases suffering from this disorder, and the pathology of 1 case that came to autopsy. The pathologic findings included not only the commonly found intracellular amyloid (Lafora) bodies, but also material with similar staining properties in cardiac muscle and in liver cells, a feature reported for the first time.

The cases occurred in three separate families, and in each family within the same generation. The genetic pattern, investigated by A. C. Stevenson, was that encountered in rare single-gene recessive inheritance. The clinical features consisted of more or less continuous myoclonus, bilateral, irregular, and asymetrical, interrupted at times by major epileptic fits. In two families the onset was with fits and myoclonus simultaneously. In the third, the myoclonus did not make its appearance until the beginning of the terminal stage. Formal tests of coordination as with any voluntary movement increased the myoclonus and produced an intention tremor simulating that of advanced multiple sclerosis. The age at onset was 14 years in family A, between 7 and 14 in family B, and in family C much later, between 19 and 27 years. The electroencephalogram showed in all patients bilaterally synchronous sharp waves, surprising in view of the asymmetry of the myoclonus. The interval between the cortical discharges and the electromyographic discharges in the affected limbs was short, suggesting that the myoclonus originated not cortically but in the brain stem.

In the autopsied case, there were numerous Lafora bodies within and without nerve cells throughout the neuraxis. Their morphology was like that already described in earlier cases. Although universally distributed, they were at their largest in the substantia nigra. Here they were seen as spheres up to 20$\mu$ in diameter, with a central star-shaped "fissure." Large bodies were also found in the dentate nuclei. The material in the heart occurred as irregular basophilic deposits within cardiac fibers. The deposits in the liver cells formed circles or halos around the liver cell nuclei. The Lafora bodies and the deposits in heart and liver parenchyma were examined histochemically.

Not all cases of progressive myoclonic epilepsy show intracellular Lafora bodies. From the literature, cases may be classified pathologically into three groups. These are: (1) Lafora body group (11 examples). (2) Lipoid inclusions group (4 examples). A few cases of amaurotic family idiocy present with this syndrome. (3) Degenerative disease group (10 examples). The nature of the degenerative change is obscure. In some, as in Hunt's case of "dyssynergia cerebellaris myoclonica," there was atrophy of the efferent dentate system.

The finding of visceral deposits suggests that in the Lafora body group, the basic disease process may be generalized and may be a disorder of intracellular carbohydrate metabolism. Investigation of the remaining cases, including serum electrophoresis for proteins and lipoids and urinary chromatograms for carbohydrates and amino acids, showed no significant abnormality, but the hypothesis remains valid. Since this paper was published, a second case with similar visceral deposits has come under observation in Vienna (F. Seitelberger, personal communication, 1955). 45 references. 14 figures. 3 tables.—*Author's abstract.*

## DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

68. *Cervical Myelopathy; a Contribution to Its Pathogenesis.* EDWIN CLARKE AND J. H. LITTLE, London, England. Neurology 5:861–867, December, 1955.

It is a well-known fact that chronic degenerative changes in the cervical spine (cervical spondylosis) are universal in elderly persons. However, spinal cord compression produced by this condition (cervical myelopathy) is relatively rare, and at the moment its pathogenesis is imperfectly understood. It is possible that several factors are operative, and in this paper a case is reported that illustrates two of them.

The patient was a woman of 81 years who developed a quadriplegia over a period of five years and at autopsy was shown to have a very severe compressing lesion at the level of the second to third cervical vertebrae.

Because of a congenital smallness of the laminae of the second cervical vertebra, instability at the $C_2$–$C_3$ level had developed with accompanying disc degeneration and osteophyte formation resulting in compression of the anterior surface of the spinal cord. In addition, the laminae of the second cervical vertebra and its attached ligamentum flavum protruded into the spinal canal posteriorly and compressed the posterior cord surface. Severe compression between these two lesions resulted.

This case suggests therefore that (1) congenital anomalies of the cervical spine may induce local spondylosis and cord compression and (2) in cervical myelopathy, pressure on the spinal cord from behind at the same level as the anterior lesion is an important factor in the production of this condition. 29 references. 8 figures.—*Author's abstract.*

69. *Variations in the Plasma Fibrinogen During the Course of Disseminated Sclerosis.* IB PERSSON, Copenhagen, Denmark. A.M.A. Arch. Neurol. & Psychiat. *74*:17–30, July, 1955.

On the basis of Putnam's theory that the characteristic plaques in disseminated sclerosis are caused by thrombi in the small veins of the central nervous system, investigations have been made with a view toward demonstrating factors that might explain the origin of these thrombi. A rise in the plasma fibrinogen has been previously demonstrated in disseminated sclerosis. This is of special interest in this connection, as a raised fibrinogen content appears in thrombotic conditions.

The investigations comprised 16 patients with multiple sclerosis and seem to indicate that variations of the plasma fibrinogen occur in disseminated sclerosis and that exacerbations of the disease are accompanied by rises in the plasma fibrinogen. This gives rise to the question of what importance may be ascribed to the plasma fibrinogen in the case of thrombus formation in plaques. Several conditions, however, seem to argue against a possible consideration that fibrinogen in this process is of primary importance. Thus, often an increased fibrinogen occurred without clinical signs of the formation of new plaques. The increase of plasma fibrinogen is, moreover, found in other chronic diseases without this giving rise to an increased frequency of thrombus formation. The periodically increased plasma fibrinogen content and the clinically demonstrable exacerbations are most likely to be incidental to the actual cause of the disease. 25 references. 16 figures.—*Author's abstract.*

70. *Intellectual and Affective Functions in Multiple Sclerosis.* ALEXANDER T. ROSS AND RALPH M. REITAN, Indianapolis, Ind. A.M.A. Arch. Neurol. & Psychiat. *73*:663-677, June, 1955.

Widely divergent estimates have been reported of the incidence and severity of intellectual impairment in multiple sclerosis. This investigation proposed to evaluate intellectual and affective functions in a group of patients with multiple sclerosis as compared with a control group of patients with verified brain damage and an additional control group composed of patients without brain damage but most of whom were neurotic. Individual patients in each group were matched on the basis of color, sex, age, education, and the Wechsler-Bellevue Intelligence Quotient in an attempt to control possible sources of variance irrelevant to the problem. Psychologic tests were individually administered to each patient and scored by a person other than the writers. These included the Minnesota Multiphasic Personality Inventory, Halstead's tests for measuring biologic intelligence, and the Rorschach test. Statistical intergroup comparisons were made of the quantitative results.

The results on the Minnesota Multiphasic Personality Inventory gave typical "neurotic" profiles for each group. The profiles were remarkably similar, indicating the prevalence of neurotic-like complaints and symptoms among patients with multiple sclerosis and other types of brain damage. Halstead's tests showed substantial impairment of adaptive abilities dependent on brain functions in both the brain-damaged and multiple sclerotic groups, with the neurotics falling generally in the normal range. The Rorschach test also showed very similar results in the groups with multiple sclerosis and verified brain damage, with the neurotic group obtaining considerably better mean scores. Although the groups were small, many of the differences between the groups without brain damage and multiple sclerosis were statistically significant. The groups with verified brain damage and multiple sclerosis, however, were very similar throughout the comparisons. The results suggest that, in addition to persons with affective disturbances primarily of a neurotic-like character, impairment of intellectual functions occurs in a high proportion of persons with multiple sclerosis. Cognizance of these facets of the disease should be valuable to the physician in assisting the patient to adjust to his problem with maximal efficiency within the framework of his limitations. 43 references. 4 figures. 6 tables.—*Author's abstract.*

## DISEASES AND INJURIES OF THE SPINAL CORD AND PERIPHERAL NERVES

71. *Amyloid Polyneuropathy.* JOHN F. SULLIVAN. THOMAS E. TWITCHELL, GHERARDO J. GHERARDI, AND WILLARD P. VANDER LAAN, JR., Boston, Mass. Neurology *5*:847-855, December, 1955.

This is a report of 3 cases of chronic progressive sensory motor polyneuropathy associated with proved primary amyloid disease. The patients were all in the fifth decade, and all presented a similar picture of involvement of several systems. All the patients complained of hoarseness, and examination of the larynx in 2 patients revealed a thickening of the vocal cords and amber discoloration in 1 and laryngeal polyps in another (which on biopsy

revealed an amyloid tumor). All the patients revealed evidence of cardiac involvement; 1 had congestive heart failure; the other showed nonspecific electrocardiographic changes. All the patients revealed a symmetrical relentlessly progressing polyneuropathy with onset in the lower extremities, but soon involving also the upper extremities. Diagnosis of amyloid disease was confirmed in 1 on autopsy. Diagnosis in the others required repeated biopsies and detailed study of biopsy material.

It is concluded that a clinical diagnosis of amyloid polyneuropathy of the nonfamilial type can be made on the basis of chronic progressive polyneuropathy associated with cardiac involvement and hoarseness. 19 references. 7 figures.—*Author's abstract.*

## ELECTROENCEPHALOGRAPHY

72. *The Electroencephalogram in Cerebral Atrophy.* ANTONIO BALESTRIERI, LOUIS GREENSTEIN, AND HANS STRAUSS, New York, N. Y. Am. J. M. Sc. *230*:178–181, August, 1955.

Electroencephalograms were obtained on 100 cases of cerebral atrophy that had been verified by pneumoencephalography. Abnormal electroencephalograms were found in 51 cases and normal records in 49. Of the 51 abnormal records, 21 showed focal abnormality, which in 12 consisted of irregular delta activity. In these 12 cases, the etiology of the atrophy was either cerebrovascular disease or trauma. Only in 4 cases was the focal abnormality of a high degree. All these patients had epileptic attacks. No record with a high degree of focal abnormality was found in a case with cerebral atrophy without epilepsy. Therefore, a record with a high degree of focal abnormality in a patient without epileptic attacks must suggest an expanding lesion rather than cerebral atrophy, even if there is a history of cerebral trauma or a history suggesting a cerebrovascular accident. 10 references. —*Author's abstract.*

73. *Incidence of Seizures, with EEG Findings, in Prefrontal Lobotomy.* MAURICE KLOTZ, St. Cloud, Minn. A.M.A. Arch. Neurol. & Psychiat. *74*:144–148, August, 1955.

A survey was made of the incidence of seizures before and after prefrontal lobotomy in 180 patients subjected to 193 operations at Veterans Administration Hospital, St. Cloud, Minnesota, from March, 1946, to February, 1955. Data were obtained on 100 patients, of whom 83 met the minimum time of six months to more than four years. Seizures of the grand mal type occurred in 19 per cent of the patients previously seizure-free, and 59 per cent of the group were self-limiting without medication. The times of the seizures occurring for the first time were from the postoperative period to 39 months later. Electroencephalographic abnormalities were noted in 18 per cent of the patients before the operation and in 78 per cent of the patients directly after. These were primarily of the S-3 type, mostly in frontal areas, especially the right. There were usually no significant prognostic relationships between the electroencephalographic abnormalities and the incidence of seizures. There was some relative improvement noted in patients with seizures preoperatively after lobotomy. The electroencephalographic abnormalities improved rapidly in the first four months postoperatively, and then gradually improved almost completely by the fourth year. 19 references. 2 figures. 4 tables.—*Author's abstract.*

## INFECTIOUS AND TOXIC DISEASES OF THE NERVOUS SYSTEM

74. *Actinomycosis of the Brain; Report of a Successfully Treated Case.* A. P. BARTER AND M. A. FALCONER, London, England. Guy's Hosp. Rep. *104*:35–45, 1955.

The authors describe the case of a girl aged 22 who first presented with meningitis without localizing signs. Her spinal fluid contained excessive numbers of cells, polymorphonuclear leukocytes predominating; culture was sterile and no fungi were seen on roentgenograms. She was treated as a possible tuberculous meningitis patient but later developed a left hemiparesis and raised cerebrospinal fluid pressure. Ventriculography and arteriography demonstrated the presence of a right temporal lobe abscess. This was completely removed. The patient recovered with, however, a residual left hemiparesis and homonymous hemianopia. Sections of the multilocular abscess showed *Actinomyces israeli*, and the organism was grown on anaerobic culture. Despite exhaustive investigations, no primary focus from which the abscess might have arisen could be found.

In the discussion, 148 previous cases of actinomycosis of the central nervous system are noted, of which only 7 recovered (2 meningitis, 5 abscess). They are divided into three groups: (a) 38 as a result of direct spread from a contiguous lesion in the head and neck; (b) 86 following hematogenous spread from lesions elsewhere in the body; (c) isolated lesions, as in this case, in which no other site of actinomycosis can be found. Some of these present as a brain abscess, others as a tumor of the third ventricle. Diagnosis may be difficult but should be considered in cases of nonbacterial pyogenic meningitis accompanied by a polymorphonuclear leukocytosis. 34 references. 2 figures.—*Author's abstract.*

## TREATMENT

75. *Long Range Treatment of Multiple Sclerosis with Pancorphen.* JOSEPH WILDER, New York, N. Y. J. Nerv. & Ment. Dis. *121*:545–552, June, 1955.

The author has reported in previous publications on various aspects of short-range treatment of multiple sclerosis by a series of five intravenous injections of Pancorphen in 150 cases. Pancorphen is an extract of heart muscle digested by pancreas with phenol added. It is characterized by immediate reactions among which focal neurologic responses and vasodilating effects are most pronounced. In the present study the author reports on 13 cases treated periodically for four to nine years with 4 to 26 series of Pancorphen. He does not believe that the treatment produces a cure, arrests the disease, or protects from relapses. Partial remissions, however, are obtained even in old and advanced cases; repeated treatments influence the course of the disease favorably; the progressive type of remission is more frequent, and the duration of attacks is shortened. The results are best if the treatment is given in the beginning of an attack. The recommended procedure for long-range treatment is: a series of five injections three to four times a year plus extra emergency treatment in case of new symptoms. Strict individualization of doses and intervals according to the author's description is a condition for success. 6 references. 2 figures.—*Author's abstract.*

76. *Trigeminal Neuralgia; Treatment by Surgical Decompression of Posterior Root.* ROBERT DEAN WOOLSEY, St. Louis, Mo. J.A.M.A. *159*:1713–1718, December 31, 1955.

Forty-five patients were operated on according to the decompression procedure described by Taarnhøj in 1952. None of these patients has needed nerve sections, subsequently. It was emphasized that the diagnosis of trigeminal neuralgia should be limited to those people who have sudden onset of pain, sharp, shooting pain of the trigeminal nerve, and sudden disappearance of pain. If the diagnosis is limited to such patients, the operative procedure will give the desired results. It was emphasized that the decompression procedure is the one of choice with patients of ophthalmic division neuralgia. In conclusion, it was stated that it is too early to be able to say how many patients undergoing such decompression will have to be subjected to nerve root section for final relief of pain. Until the procedure can be finally evaluated, the decompression procedure seems preferable to nerve-severing techniques. 18 references. 2 figures.—*Author's abstract.*

## INTRACRANIAL TUMORS

77. *Intracranial Neoplasms in Psychotic Patients; Survey of 2,430 Consecutive Complete Autopsies Performed by the Boston State Hospital during the Period 1930–1950.* NAOMI RASKIN, Boston, Mass. Am. J. Psychiat. *112*:481–484, January, 1956.

As deaths due to malignant tumors are being reported on the increase in the general population and to a lesser degree in the mental hospitals, while deaths due to syphilis and tuberculosis have greatly declined, it was thought that a survey of a large number of consecutive autopsies performed at the Boston State Hospital and compared with similar surveys at other state and general hospitals might be of interest. A survey of 2430 consecutive autopsies during the period 1930–1950 was made and the findings tabulated. Meningiomas formed the largest group in the state hospitals, and gliomas were much higher in the general hospitals. Most of the undiagnosed intracranial tumors were found in aged patients with severe cerebral arteriosclerosis. 17 references. 2 tables.—*Author's abstract.*

## BOOK REVIEWS

*Administrative Medicine—Transactions of the Third Conference, 1954.* Edited by GEORGE S. STEVENSON. New York, Josiah Macy Jr., Foundation, 1955. Pp. 172. Price $3.00.

This is another in the ever-growing series of Macy Foundation Conference Reports—a program described by Dr. Frank Fremont-Smith, the Medical Director, as "an experiment in communication." The present volume deals with medical administration in general under the headings: Special Characteristics of Medical Administration Problems (which make them different from other fields of administration); Distinctive Characteristics and Educational Requirements; The Hospital and Its Relationship to the Community; Principles and Concepts of Business Administration as Applied to Medical Administration; Administration as a Tool and Technical Knowledge as a Guide; Administration Problems of the Community as a Whole.

The participants (25, including guests) represented a variety of disciplines concerned with the topic, and the free discussion reproduced in the book is interesting and instructive.

—*Winfred Overholser, M.D.*

*The Physician and the Law.* ROWLAND H. LONG. New York, Appleton-Century-Crofts, Inc., 1955. Pp. 284. Price $5.75.

This book can well be read by any physician. Within a brief compass are the answers to many legal questions and suggestions for avoiding pitfalls. Such topics as malpractice and defenses to the charge, commitment of the mentally ill, blood group tests, artificial insemination, the physician and the criminal law (abortion, contraception, narcotics, dying declarations, etc.), privileged communications, and expert testimony are succinctly and authoritatively dealt with. The chapters are followed by numerous references to legal decisions and books.

Mr. Long is an attorney; he has been aided, however, by Drs. Alexander Weiner and Milton Helpern, so that the volume presents an approach that is helpful to the physician to whom it is addressed, rather than too strictly a legalistic one.

Mr. Long has performed a useful service to the medical profession.

—*Winfred Overholser, M.D.*

*Management of Addictions.* EDITED BY EDWARD PODOLSKY, M.D. New York, Philosophical Library, 1955. Pp. 413. Price $7.50.

This book, poorly edited, exhibits glaring errors in spelling and construction that here and there annoy the reader and convey the impression that the treatise cannot be a serious and authoritative report on the subject of alcoholism and drug addiction.

The book is divided into two parts: the first 26 chapters are devoted to alcoholaddiction, and the last nine chapters to drug addiction. Forty-eight contributors are responsible for the 35 chapters of the book. Although the subject matter is presented in an eclectic manner, too many chapters are devoted to lengthy presentations of the various medicinal adjuncts in the management of the alcoholic patient. A version treatment, disulfiram (antabuse) hormones, barbiturates, carbon dioxide, and even hypnosis are given a chapter or two in the alcohol addiction section of the book.

Although the book aims at giving accent to the management of the individual patient, a textbook on the subject of alcoholism and drug addiction should not leave out Public Health consideration of rehabilitation, education, and research activities in these fields. A chapter on the legal facets of the problems could very well have been included. Fortunately, upon careful reading of the many chapters, statements are made by the many authoritative writers that alcoholism and drug addiction are Public Health problems requiring broad planning at the community level to bring about the constructive teamwork necessary for the rehabilitation of alcoholic and drug addict patients. Discussion of Federal aid versus local aid for the control of alcoholism and drug addiction is not presented. The epidemiology of alcoholism and drug addiction is not sufficiently delineated in this book to help in the organization of programs for the community (white collar) alcoholic versus the skid road alcoholic and the derelict drug addict versus the drug addict who continues to function

socially. The absence of a detailed discussion of Alcoholics (and Narcotics) Anonymous is surprising indeed.

Several chapters in the book present the theoretic and clinical aspects of the problems of alcoholism very brilliantly, particularly the chapters on psychodynamics and the chapter on "Therapeutic Success in Alcoholism." The chapter on "Construction Teamwork in the Treatment of Alcoholism" emphasizes a basic consideration in the management of the alcoholic patient. The follow-up study of "Results in Hospital Treatment of Drug Addictions" gives emphasis to the importance of follow-up information that is so lacking, particularly in the cases that have passed through the U. S. Public Health Service Hospital in Lexington, Kentucky.

This book hardly presents a well-organized treatise on the management of addictions in the light of current developing clinical trends in the fields of alcoholism and drug addiction as Public Health problems. As a textbook, it fails to present the subject matter in a way to facilitate orientation into the problems alcoholism and drug addiction pose as complex social and psychobiologic disorders. The successful management of these addictions rests upon such orientation. The book for the most part emphasizes the variety of medical techniques that physicians here and there empirically employ in attempting to treat individual patients with alcoholism and drug addictions. Interesting as these explorations might be, the few chapters on the psychodynamics and psychotherapy of the addictions were, to this reader, the most useful part of the book.—*A. Zappala, M.D.*

*Neuropharmacology: Transactions of the First Conference.* Edited by HAROLD A. ABRAMSON. New York, Josiah Macy Jr., Foundation, 1955. Pp. 210. Price $4.25.

This book contains the proceedings of the First Conference on Neuropharmacology which took place in May 1954 at Princeton, New Jersey. Five major topics are presented: Consideration of the Effects of Pharmacological Agents on the Over-All Circulation and Metabolism of the Brain (Seymour S. Kety); Functional Organization of the Brain (Ernest A. Scharrer); Studies of Electrical Activity of the Brain in Relation to Anesthesia (Mary A. B. Brazier); Ascending Reticular System and Anesthesia (Horace W. Magoun); Observations on New CNS Convulsants (Carl C. Pfeiffer).

Everyone who has followed the rapidly increasing development of electrochemical and histochemical methods as employed in studies on cellular metabolism under biologic conditions will enjoy part I. The theoretic fundamentals and critical examination of old and new methods are presented in sufficient detail, along with data from experiments.

In part II, the role of mitochondria as carriers of enzymes and the possibility of a positive relationship between vascularity and the number of mitochrondria present in the cell is entertained.

The presentation and discussions in part III are rather long and somewhat detailed. The electrical activity of the brain, as measured with the electroencephalogram, and the electrographical effect of barbiturates is discussed in some detail, along with a rather large amount of experimental data.

In part IV, experimental data are presented whereby electrocortical arousal to afferent stimulation was not mediated by the classic route to the sensory cortex. It is postulated

that collateral connections reach the cortex by nonspecific channels, involving intracellular enzyme systems.

Part V presents a stimulating description of how a new fluorescent convulsant dye was employed to study the permeability of cell membranes and raise new questions on the intracellular organization of the metabolic process.

Each topic contains a detailed bibliography at its end. Typographical errors are few. In this valuable and interesting symposium, 20 specialists discuss various trends and aspects of contemporary electrochemical and histochemical research.

This book is to be recommended as a stimulating, and, in some instances, brief analysis of a very complex active research area.—*James D. Solomon, M.D.*

*A Handbook of Hospital Psychiatry: A Practical Guide to Therapy.* LOUIS LINN, M.D. New York, International Universities Press, 1955. Pp. 560 + XXII. $10.00.

This is a useful and comprehensive book. Indeed, it should be required reading for all psychiatric residents and junior staff members.

The author is a psychoanalytically trained psychiatrist now on the staff of Mt. Sinai Hospital, New York City, who has had state hospital and Army psychiatric hospital experience. He approaches the problem primarily as one interested in therapy and in the contribution that the various activities of a mental hospital can make to the patient's progress. As he well says (p. 27), "there is no detail of hospital life that does not contain within it therapeutic possibilities."

The book is divided into five general parts: The Treatment Program, The Treatment Team, The Patients, The Hospital, and The Community. In addition there are five appendices, namely, Preliminary Psychiatric Formulation, Reading Materials for Group Bibliotherapy, Characterologic Inventory, Home Training Program for Retarded Children, and Classification of Mental Disorders.

The various types of patients, ancillary therapy, and treatment are discussed. The importance of architecture, staff education, research, psychiatric services in general hospitals, and outpatient and family care are treated briefly but effectively. Each chapter is followed by a selected bibliography, each item being annotated in a few words.

A book of this sort, comprehensive as it is, can hardly be expected to cover all aspects equally well. The author is, for example, a bit patronizing as to somatotherapy, though oddly more tolerant of lobotomy than are many nonanalysts. This is but a minor point, however, in comparison with the integrative approach to the multifaceted problems of hospital psychiatry.

The volume covers a wide field and meets a need that has long been felt by those who are engaged in hospital practice. Our thanks go to Doctor Linn.—*Winfred Overholser, M.D.*